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# Aza-enolate alkylation reactions of lactim ethers

Taylor, Piers

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# *Aza*-enolate alkylation reactions of lactim ethers

Piers Taylor

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

2005

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# Contents

# Acknowledgments

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Finally I would like to thank Dr. Steven Bull, Celltech and the EPSRC for the opportunity to undertake a PhD position, in particular I would like to thank Dr. Steven Bull for everything I have learnt from him in the last few years.

Dedicated with love to the memory of

John and John Bradbury and Nora Taylor

# Abstract

Lactim ethers represent a labile and extremely applicable substrate for the formation of a wide variety of heterocyclic compounds. This thesis is dedicated to the development of methodologies relating to the alkylation, transesterification and isotopic labelling of the lactim ether functionality.

The first chapter of this thesis discusses the background reactions that lactim ethers readily undergo, and their applicability in the field of heterocyclic chemistry, and therefore also in the arenas of drug discovery and natural product synthesis.

The second chapter reports on the development of lactim ether alkylation strategies for the synthesis of α-alkyl lactim ethers, which are shown to proceed in high and reliable yields for a wide range of electrophiles. The applicability of this work is shown through the use of the newly formed α-alkyl lactim ethers to produce a series of α-alkyl lactams and ω-amino esters.

The third chapter of this thesis concentrates on the development of a chiral alkylation strategy that proceeds in an analogous way to the alkylation systems reported in the second chapter.

The fourth chapter of this thesis describes work extending Schöllkopf's *bis*-lactim ethers methodology to include the regioselective isotopic labelling of the *bis*-lactim ether in order that it may be used to produce enantiopure isotopically labelled substituted phenylalanines. Also described in this chapter is research detailing the production of orthogonally protected *O*-methyl *O*-benzyl Schöllkopf's *bis*-lactim ethers that once hydrolysed would allow facile separation of the chiral auxiliary fragment form the newly formed α-alkyl amino ester.

# Chapter 1

# Introduction

# Chapter 1.

## 1.1. Introduction

This research thesis describes the use of lactim ether substrates in synthesis, concentrating on the development of efficient strategies for the alkylation of the *aza*-enolates of lactim ethers and its application to the asymmetric synthesis of isotopically labelled α-amino esters. Consequently, the following chapter discusses the role of heterocycles in organic chemistry, and provides as overview of the range of methods employed for the synthesis of lactim ethers, and their use as building blocks for synthesis.

## 1.2. Heterocycles in Organic Chemistry

Heterocycles represent a widely used class of compounds in Nature and are frequently utilised as building blocks in synthetic chemistry, with over half the compounds listed in *Chemical Abstracts* being derived from heterocyclic compounds.

Heterocyclic compounds are essential to life, playing vital roles in metabolism in all living cells, for example the pyrimidine and purine bases of DNA, the essential amino acids proline, histadine and tryptophan, and sugars and oligosaccharides. (Figure 1.2.1.)

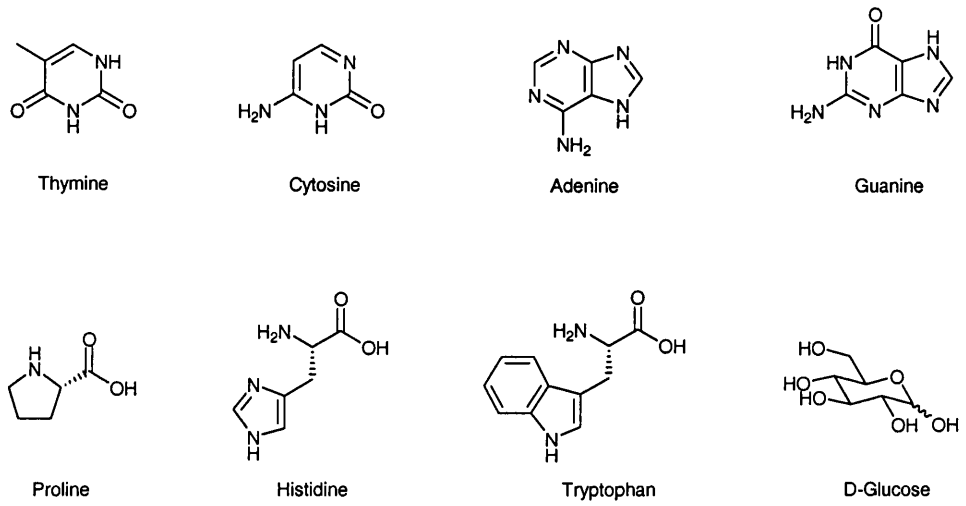



**Figure 1.2.1.** Heterocycles that play a key role in living systems.

To become effective pharmacologically active species compounds must be readily absorbed by the host organism, and therefore must be soluble in aqueous media. The presence of heteroatoms helps facilitate solvation of organic compounds in aqueous media, with nitrogen being the most commonly used atom for the construction of heterocyclic compounds due to its basic nature. When treated with acid, many heterocycles containing nitrogen atoms form their corresponding salts, resulting in reduction in the compound's lipophilicity, thus increasing its solubility in aqueous media, and improving its bioavailability. (Figure 1.2.2.)

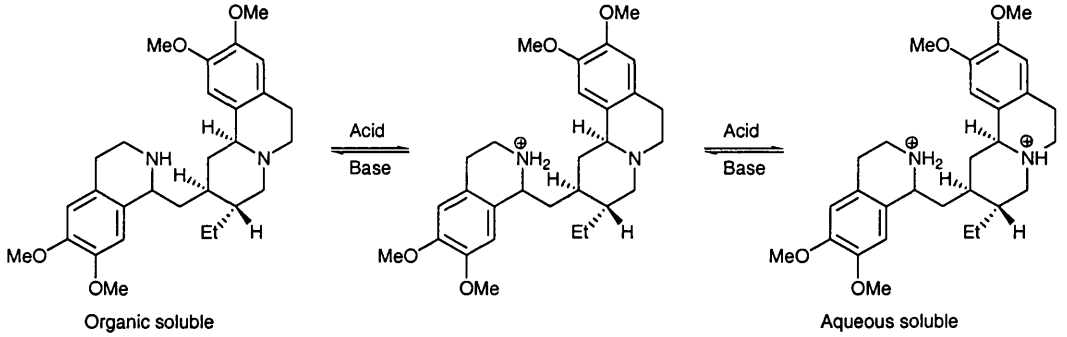



**Figure 1.2.2.** Protonation of emetine to its diammonium salt.

As a result nitrogenous heterocycles often demonstrate excellent pharmacological activity, for example, penicillins and cephalosporins are superb antibacterial agents, whilst the alkaloid morphine, is a potent analgesic. (Figure 1.2.3.)

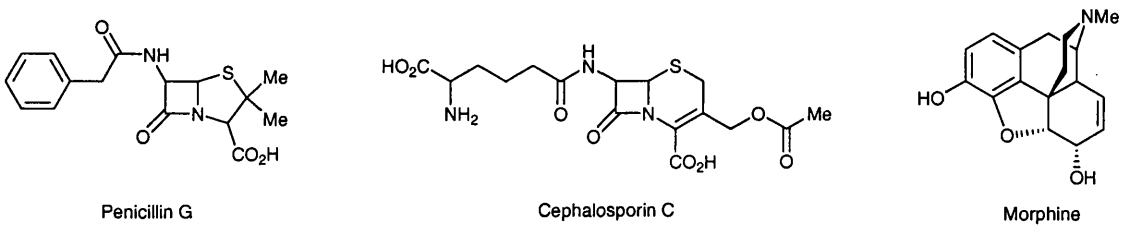



**Figure 1.2.3.** Structures of penicillin G, cephalosporin C and morphine.

Compounds demonstrating biological activity often undergo rigorous structure activity optimisation studies before they are deployed as pharmaceuticals. Thus, many features of a lead compound are varied during this optimisation stage to increase levels of biological activity. Most heterocyclic molecules are prepared by multicomponent

syntheses that result in the incorporation of a plethora of different functional groups, with rigid heterocyclic molecules being ideally suited as building blocks for generating the desired levels of diversity within a library of pharmacological compounds.

Nitrogen containing heterocycles represent one the most commonly used pharmacophores in drug discovery. For example, pyridines are aromatic heterocycles present in many active compounds such as nicotine, which is as an anthelmintic and an agricultural insecticide, whilst vitamin $B_6$ contains a pyridine fragment that plays an important role in metabolism, and the cinchona alkaloids, such as cinchonine which have been used as anti malarial drugs and as catalytic chiral ligands for asymmetric synthesis. (Figure 1.2.4.)

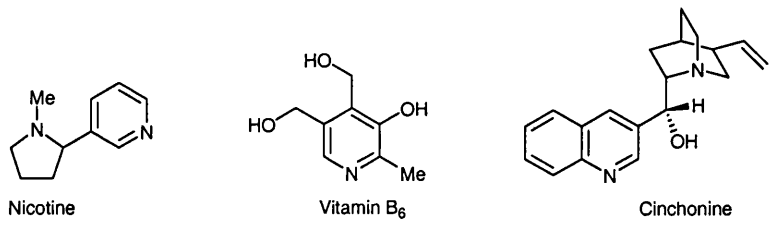



**Figure 1.2.4.** Structures of nicotine, vitamin $B_6$ and cinchonine.

Piperidines also represent an important structural motif in both natural compounds and synthetic drugs that display a wide range of biological activities. For example, naturally occurring alkaloids such as anabasine act as insecticides, whilst synthetic species (1*S*,2*S*)-2-methylpiperidinyl-3-cyclohexen-1-carboxamide acts as a potent insect repellent. As a result many stereoselective syntheses have been developed for the preparation of chiral polysubstituted piperidines. (Figure 1.2.5.)

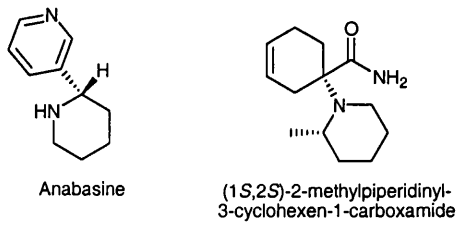
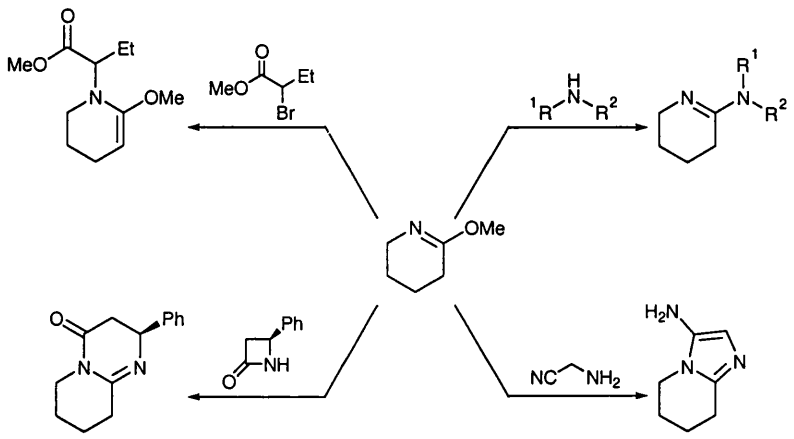



**Figure 1.2.5.** Structure of anabasine and (1*S*,2*S*)-2-methylpiperidinyl-3-cyclohexen-1-carboxamide.

Lactim ethers represent a class of compound that are well suited to the synthesis of highly functionalised nitrogen containing heterocycles, since they possess both electrophilic and nucleophilic character, which may act individually or in tandem to great effect. (Scheme 1.2.1.)

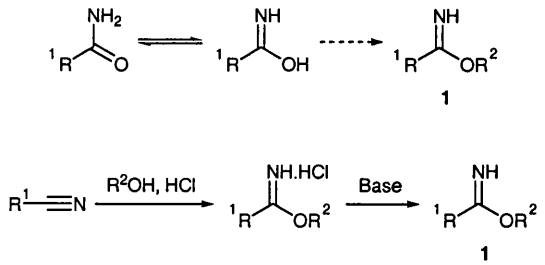


**Scheme 1.2.1.** Representative range of reactions using a lactim ether building block.

This thesis is concerned with the development of *aza*-enolate alkylation methodology using lactim ether substrates and as a consequence a comprehensive review of the chemistry of this class of compound now follows.

## 1.3. Nomenclature of imino ethers and lactim ethers

Neilson provided an apt description of imino ethers in 1975 when he stated that 'imino ethers are esters of the hypothetical imidic acids',[1] as shown for the Pinner synthesis of imino ether **1**. (Scheme 1.3.1.)



**Scheme 1.3.1.** Neilson's description of an imino ether **1**.

With respect to Neilson's description there exists a huge range of potential isomeric forms of imino and lactim ethers that may be accessed through formation of cyclic structures, or incorporation of the imino ether functionality within a ring. (Figure 1.3.1.)

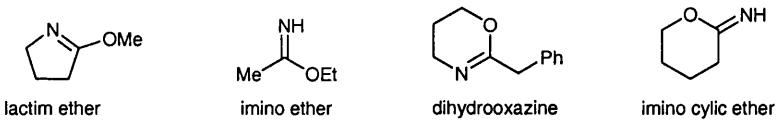



**Figure 1.3.1.** Isomers of imino and lactim ethers.

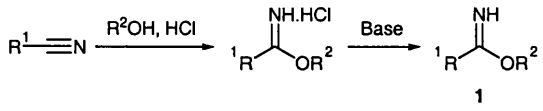
Naturally as the structures of the resultant heterocycles differ so do their properties, and as a result a vast amount of literature precedent exists that deals solely with the preparation of lactim ethers and imino ethers.

## 1.4. Methods commonly employed for the synthesis of imino ethers and lactim ethers

Imino and lactim ethers have been prepared by a variety of synthetic protocols with initial reports having appeared over a century ago. A review of the most commonly employed methods for their synthesis now follows.

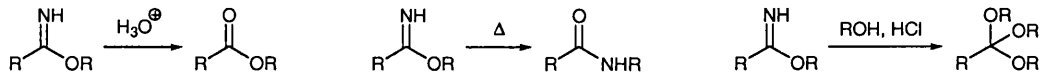
### 1.4.1. Pinner synthesis

The Pinner synthesis is the most obvious and direct method for the formation of imino ethers. The protocol involves the action of a strong mineral acid upon a nitrile to activate it towards nucleophilic attack by an alcohol on heating. Beckurts and Otto first attempted this reaction in 1876,[2] however the structure of the resultant product was not determined until the pioneering work of Pinner in 1892,[3] who performed an in depth investigation of this methodology. (Scheme 1.4.1.)



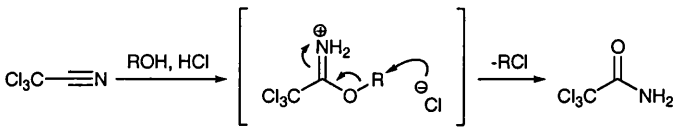

**Scheme 1.4.1.** Pinner synthesis of a generic imino ether **1**.

Whilst the Pinner synthesis is still widely employed for the synthesis of imino ethers it is well known that it suffers from a range of competing side reactions. The reaction must be performed under anhydrous conditions as imino ethers readily undergo hydrolysis under aqueous acidic conditions. Other noted side reactions include the Chapman rearrangement, involving thermal degradation of the imino ether to afford *N*-alkyl amides, and triortho ester formation as a result of excess alcohol being present. (Scheme 1.4.2.)




**Scheme 1.4.2.** Side reactions of the Pinner synthesis.

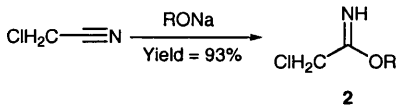
Other limitations of the reaction include the preclusion of using tertiary alcohols as nucleophiles because the imino ether product and the parent alcohol tend to undergo dehydration. Furthermore, the Pinner reaction often affords poor yields when the nitrile is sterically hindered, or when it contains a strong electron withdrawing substituent such as trichloroacetonitrile or α-nitroacetonitrile.[4] In these cases rapid decomposition of the imino ethers occurs to afford the corresponding amide *via* attack of halide anion at the alkoxy substituent. (Scheme 1.4.3.)




**Scheme 1.4.3.** Pinner synthesis using an electron deficient nitrile and its subsequent decomposition to an amide.

## 1.4.2. Base catalysed reactions of nitriles

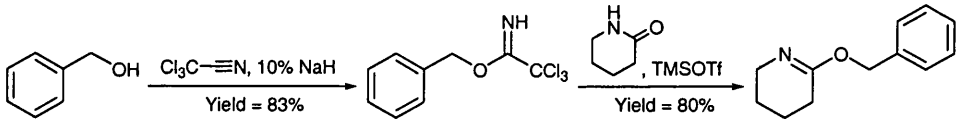
Whilst the Pinner synthesis represents a facile pathway to imino ethers under acidic conditions any nitriles that contain basic substituents will become protonated and as a consequence tedious protecting group chemistry is often required for reaction to occur. In 1961 Schaefer and Peters confirmed that there existed a complementary base catalysed pathway employing electron deficient nitriles and the corresponding alkoxide.[5] This method proceeds well for nitriles containing electron withdrawing groups, with α-chloroacetonitrile affording good yields of the desired α-chloro imino ether **2**. (Scheme 1.4.4.)




**2**

**Scheme 1.4.4.** Base catalysed formation of an α-chloro imino ether **2**.

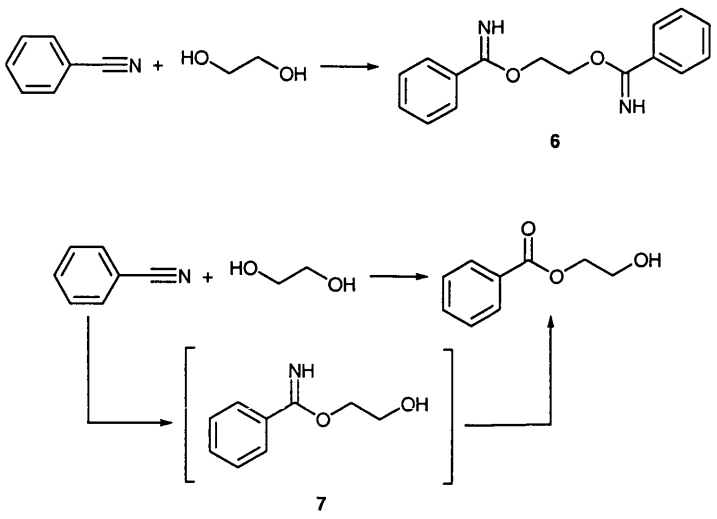
The most widely used application of this reaction is for the formation of alkyl trichloroacetimidates, since these compounds are widely utilised as mild and selective *O*-alkylating agents, with the most commonly used examples being methyl and benzyl trichloroacetimidate **3** and **4**.[6] (Scheme 1.4.5.)




**4** **5**

**Scheme 1.4.5.** Formation of benzyl trichloroacetimidate **4** and its use for the synthesis of benzyl valerolactim ether **5**.

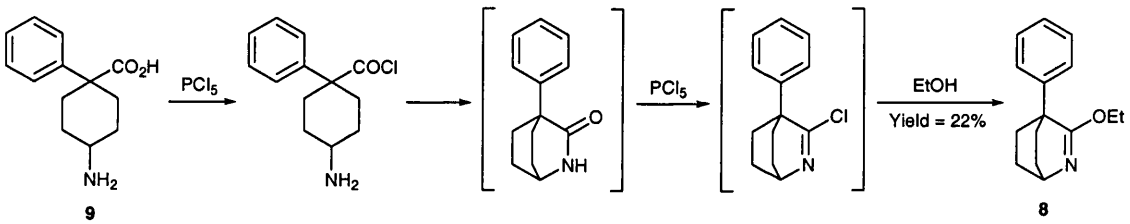
To date, little work has been described on developing a neutral analogue of the Pinner synthesis, however Robinson *et al.* did report that heating benzonitrile and ethylene glycol in a sealed tube for several days gave the corresponding *bis*-imino ether **6**, whereas heating at reflux gave an ester derived from hydrolysis of a mono imino ether intermediate **7**.[7] (Scheme 1.4.6.)




**Scheme 1.4.6.** Robinson's neutral Pinner synthesis involving reaction of benzonitile with ethylene glycol under thermal conditions.

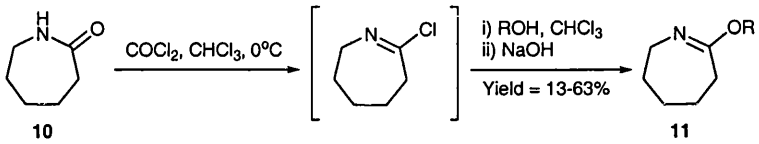
## 1.4.3. Formation of lactim ethers through addition of alcohols to iminoyl halides

Several groups have shown that cyclic amides can be transformed into imino ethers *via* iminoyl halide intermediates.[8-10] Reaction of an amide with halogenating agents such as $PCl_5$ or phosgene affords the corresponding iminoyl halide, before addition of an alcohol to gives the desired imino ether. Koelsch *et al.* demonstrated use of this pathway in 1960 for the formation of bicyclic lactim ether **8** from 4-amino-1-phenylcyclohexanecarboxylic acid, **9**, during research aimed at the production of a series of morphine analogues.[11] (Scheme 1.4.7.)




**Scheme 1.4.7.** Iminoyl halide formation and subsequent reaction with ethanol to afford a bicyclic lactim ether **8**.

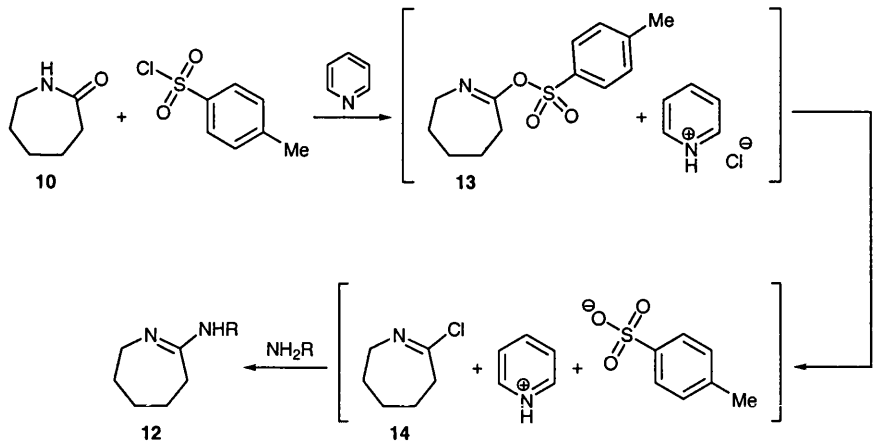
Isolation and characterisation of the intermediary iminoyl halide are not normally carried out due to their instability. For example, in a study by Jurczak *et al.* in 1982, a range of caprolactims was synthesised *via* iminoyl halide intermediates that had been generated *in situ*.[12] They treated caprolactam **10** with phosgene in chloroform, followed by addition of the appropriate alcohol to afford the corresponding lactim ether **11**. (Scheme 1.4.8.)




**Scheme 1.4.8.** Formation of lactim ethers through intermediary iminoyl halides.

It was noted that the procedure failed for tertiary alcohols and gave very poor yields for phenol, presumably as a result of the harsh acidic conditions employed in the reaction.

Some of the most compelling evidence for the formation of the intermediary iminoyl halide species came from the work of Glushkov who reported on the action of tolyl sulfonyl chloride on caprolactam **10** for the formation of amidine **12**.[13] This work corrected a previous report by Short *et al.* in 1948 who had claimed to produce amidine **12** *via* an *O*-tolylsulfonyl lactim ether intermediate **13**.[14] Glushkov however, showed that pyridinium benzene sulfonate could be isolated in high yield from the reaction mixture implying formation of the iminoyl halide **14**. (Scheme 1.4.9.)

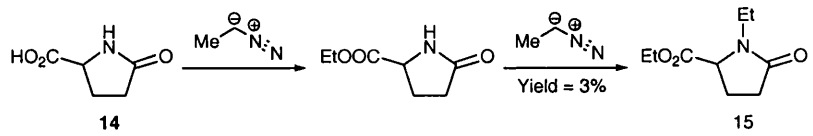


**Scheme 1.4.9.** Synthesis of amidine **12** *via* treatment of caprolactim **10** with tolylsulfonyl chloride followed by addition of an amine.

## 1.4.4. Preparation of lactim ethers through the use of diazomethane and alkyl sulfates

Until recent years the most widely reported method for the preparation of lactim ethers was through the employment of *O*-alkylating agents such as diazoalkanes and dialkyl sulfates upon the corresponding lactam.

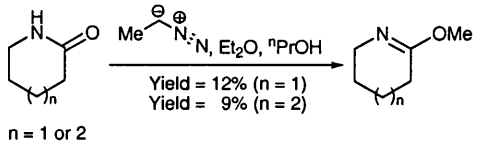
In 1961 Ralls first discovered that lactams could be *O*-alkylated *via* treatment with diazomethane (or diazoethane) during work directed towards the synthesis of carboxylic acids found in vegetable flavour.[15] Ralls was attempting to esterify the acid functionality of **14** using diazo reagents so that they could be analysed by gas chromatography. However, in the case of 5-pyrrolidone-2-carboxylic acid **14** an anomalous second compound was observed, later revealed to be the *N*-alkyl lactam **15**. (Scheme 1.4.10.)




14 15

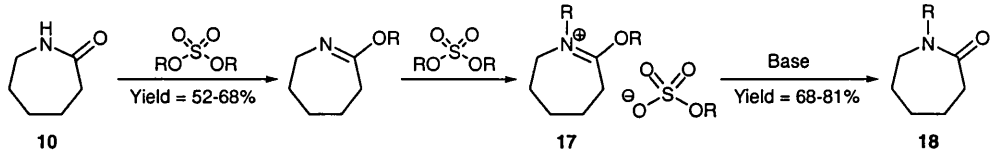
**Scheme 1.4.10.** Esterification and *N*-alkylation of 5-pyrrolidone-2-carboxylic acid **14** using diazoalkanes.

During further research Ralls demonstrated that the *N*-alkyl lactam had probably been formed *via* Chapman rearrangement of the corresponding lactim ether since performing related reactions in a mixed ethereal alcoholic solvent system afforded a 12% yield of valerolactim ether and 9% yield for caprolactim ether. (Scheme 1.4.11.)




**Scheme 1.4.11.** Lactim ether formation through addition of diazoalkanes to a lactam.

The use of dialkyl sulfates is a much more powerful synthetic procedure. The reaction generally affords excellent yields of lactim ethers, however competing *N*-alkylation products are often observed unless reaction conditions are carefully monitored. In 1948 Cairns and Benson investigated the alkylation of lactams and found that slow addition of dialkyl sulfate reagents to lactams favoured *O*-alkylation, whilst an excess of dialkyl sulfate tended to give the *N*,*O*-dialkylated imidic salt **17** that may be converted to the corresponding *N*-alkyl lactam **18** on treatment with base.[16] (Scheme 1.4.12.)

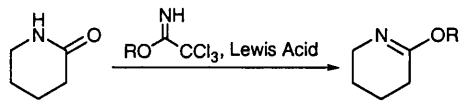



10 17 18

**Scheme 1.4.12.** *O*-alkylation of caprolactam **10** using dialkyl sulfate and subsequent *N*-alkylation to afford lactam **18**.

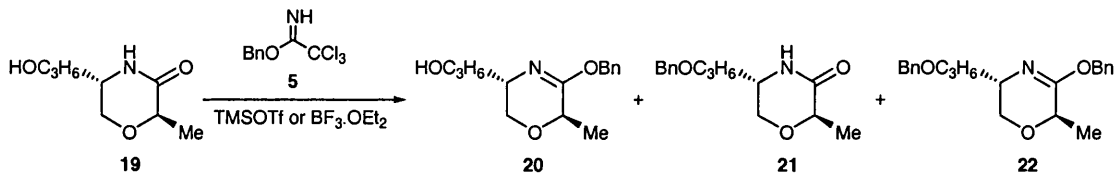
## 1.4.5. Preparation of lactim ethers through the use of alkyl trichloroacetimidates

The use of alkyl trichloroacetimidates for the synthesis of lactim ethers remains an underemployed method that represents a synthetically versatile route to a large range of lactim ether substrates. As described, trichloroacetimidates are easily synthesised *via* the action of an alcohol on trichloroacetonitrile under mild basic conditions. Primary (and secondary) trichloroacetimidates react readily under Lewis acidic conditions with cyclic secondary amides to give lactim ethers in good yield. Whilst the most notable use of trichloroacetimidate methodology is for the mild *O*-benzylation of hydroxyl groups, it has also been used for *O*-alkylation of amides. (Scheme 1.4.13.)




**Scheme 1.4.13.** Formation of valerolactim ether using trichloroacetimidate methodology.

This approach was employed in 1989 by Hönig *et al.* during the selective benzylation of a series of morpholinones for use as building blocks for the synthesis of pesticides.[6] They treated the lactam core of the hydroxy alkyl morpholinone **19** with benzyl trichloroacetimidate **4** employing a range of Lewis acids to afford the desired lactim ether structure **20** in poor to good yields (6-80%). (Scheme 1.4.14.)




**Scheme 1.4.14.** Formation of the benzyl lactim ether **20** of morpholinone **19**.

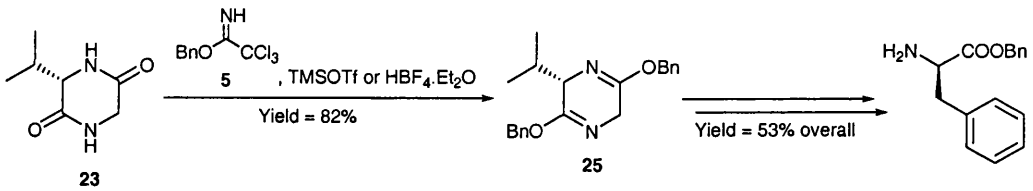
The author concluded that the use of $BF_3.OEt_2$ or TMSOTf as Lewis acids gave the most reliable and robust yields of lactim ether **20**, 70 and 80% yields respectively (entry

3 and 4, Table 1.4.1.). Under these conditions the potential formation of the competing benzyl ether lactam **21** and benzyl ether benzyl lactim ethers **22** only occurred in small yields.

| Entry | Lewis acid | % yield of lactim ether **20** | % yield of benzyl ether **21** | % yield of benzyl ether lactim ether **22** |
|---|---|---|---|---|
| 1 | TFMSA | 6 | 26 | 0 |
| 2 | TFA | 0 | 0 | 0 |
| 3 | $BF_3.OEt_2$ | 70 | 10 | 20 |
| 4 | TMSOTf | 80 | 0 | 20 |

**Table 1.4.1.** Yields of lactim ether **20** under different Lewis acidic conditions.

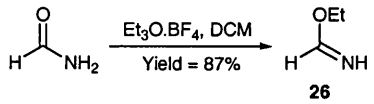
Further to this in 1993 Schöllkopf *et al.* showed that diketopiperazines could react with trichloroacetimidates to afford the corresponding dialkyl *bis*-lactim ethers.[17] Schöllkopf noted that yields for the *O*-alkylation stage of his diketopiperazine **23** were often poor, which he attributed to the poor solubility of trimethyloxonium tetrafluoroboronate **221** and the parent diketopiperazine **23** in $CH_2Cl_2$, with yields being highly dependent on the quality and consistency of the trimethyloxonium tetrafluoroboronate. As a result of these factors an alternative route to the synthesis of *bis*-lactim ether auxiliary **24** and **25** employing alkyl trichloroacetimidate was reported. Schöllkopf noted that while *O*-alkylation failed using methyl trichloroacetimidate, moderate to good yields of the *bis*-lactim ethers **24** and **25** were recorded for the ethyl and benzyl analogues (82 and 61% respectively). The group went on to lithiate the *bis*-benzyl auxiliary **25** and react it with benzyl bromide to produce enantiopure (*R*)-phenylalanine. (Scheme 1.4.15.)




**Scheme 1.4.15.** *O*-benzylation of diketopiperazine **23** using benzyl trichloroacetimidate **4**.

## 1.4.6. Preparation of lactim ethers using trialkyloxonium tetrafluoroboronates

Trialkyloxonium tetrafluoroboronates represent the most commonly used method for the synthesis of lactim and imino ethers over the last 25 years owing to the simplicity and reliability of these reactions. Despite their discovery dating back to the 1930's,[18, 19] this type of reagent was not widely employed until 1961 when Meerwein demonstrated that triethyloxonium tetrafluoroboronate could be used to convert DMF into its imino ether **26**.[20] (Scheme 1.4.16.)

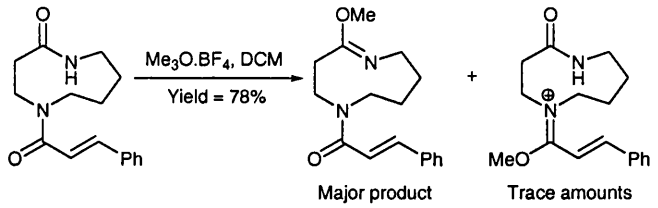



**26**

**Scheme 1.4.16.** Formation of imino ether **26** using Meerwein's salt.

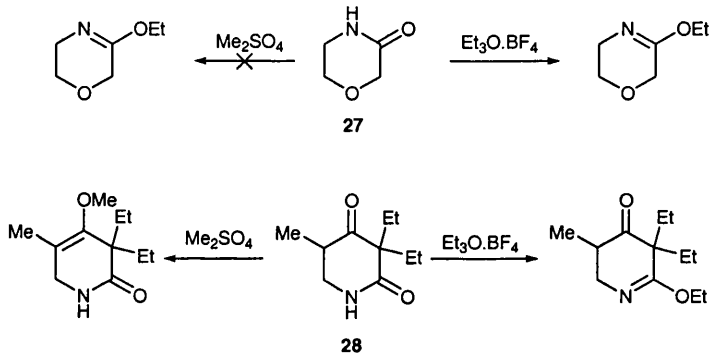
The popularity of trialkyloxonium tetrafluoroboronate methodology for the synthesis of lactim ethers has increased in recent decades, and it now represents the most common method for the preparation of lactim ethers. Trialkyloxonium tetrafluoroboronates are readily prepared, offering extremely high *O*-alkylation chemoselectivity for amides affording excellent yields of lactim ether product, having been widely used on substrates containing carbonyl, cyano and carbethoxy functionalities.[13]

In addition trialkyloxonium salts can be employed to selectively discriminate between amide groups in the same molecule. In 2002 Wasserman published a synthesis of (±)-dihydroperiphylline in which the amide group within the nine membered ring was selectively *O*-alkylated in the presence of a competing tertiary α,β-unsaturated amide.[21] (Scheme 1.4.17.)




**Scheme 1.4.17.** Regioselective lactim ether formation.

Furthermore, trialkyloxonium tetrafluoroboronate offers greater reactivity than other available reagents, e.g. *O*-alkylation of some lactams such as morpholin-3-one **27** fail completely with dialkyl sulfates, while other ketonic substrates such as 3,3-diethyl-5-methylpiperidine-2,4-dione **28** gave alternative enol ether products.[13] (Scheme 1.4.18.)




**Scheme 1.4.18.** Competing reaction pathway for alkylation of morpholin-3-one **27** and keto-lactam **28** using $Et_3O.BF_4$ and dimethyl sulfate.

## 1.5. The chemistry of imino ethers

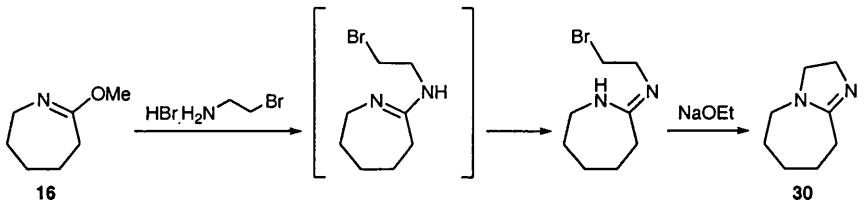
Imino ethers are labile and act as versatile synthetic intermediates owing to the range of possible reaction pathways available to them. They can act as electrophiles towards an incoming nucleophile with net replacement of their alkyloxy or imino units. Conversely, they can employ their basic $sp^2$ nitrogen atom as a nucleophile, whilst they may also be deprotonated at their α-position through the action of strong bases to afford *aza*-enolates that then react with electrophiles. They can be reduced using organometallic hydride reagents, whilst they may also be employed as alkylating

agents, where their amido character is regenerated through fission of their alkyl-oxygen bond.

## 1.5.1. Formation of amidines

One of the most useful and successful reactions of imino ethers is the replacement of the alkyloxy group with an amino group, yielding an amidine, which has been widely reported and proceeds readily with high yields.[16, 22-24] The reaction is chemoselective and may be performed in the presence of a large range of other functional groups such as esters, ketones and halogens owing to the lability of the imino ether and the subsequent stability of the amidine functionality.

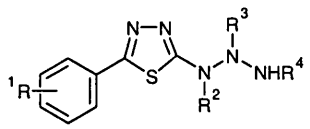
Given the facile nature of this reaction it is not surprising that this reaction was the first transformation reported for lactim ethers in 1934 by Stolle *et al.* who reported amidine formation during the synthesis of **30**.[25] Furthermore upon neutralisation of the system the authors also demonstrated the nucleophilic character of the amidic nitrogen atom by effecting a subsequent ring closure step, to afford bicyclodihydroimidazole **30**. (Scheme 1.5.1.)



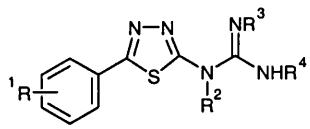

**Scheme 1.5.1.** Amidine formation followed by cyclisation to afford a dihydroimidazole **30**.

The potential of this synthetic methodology in medicinal chemistry was demonstrated in 1988 by Chapleo *et al.* who reported the synthesis of a range of novel amidines derived from simple imino ethers and amino substituted 1,3,4-thiadiazoles for use as anticonvulsant agents.[26] Previous work had shown that 2-aryl-5-hydrazino and 2-aryl-5-guanidino-1,3,4-thiadiazoles **31** and **32** showed good activity as potential

anticonvulsants, however their use was associated with undesirable side effects. (Figure 1.5.1.)



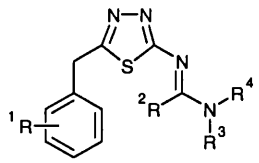
31



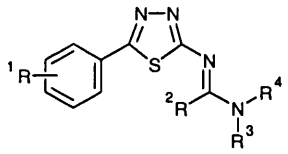
32

**Figure 1.5.1.** Structures of 2-aryl-5-hydrazino and 2-aryl-5-guanidino-1,3,4-thiadiazoles **31** and **32**.

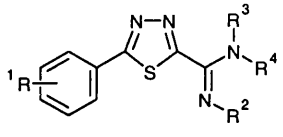
Chapleo speculated that the hydrazine functionality might be replaced by amidino groups to afford target compounds with similar anticonvulsant properties. He targeted the synthesis of both possible regioisomeric forms, i.e. **33** and **34** linked through either the amidine nitrogen atoms, or **35** linked through its central carbon atom. (Figure 1.5.2.)



33



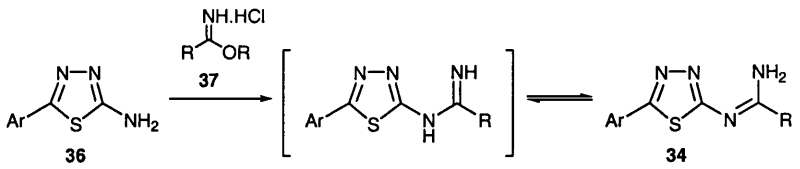
34



35

**Figure 1.5.2.** Generic isomers synthesised by Chapleo *et al.*

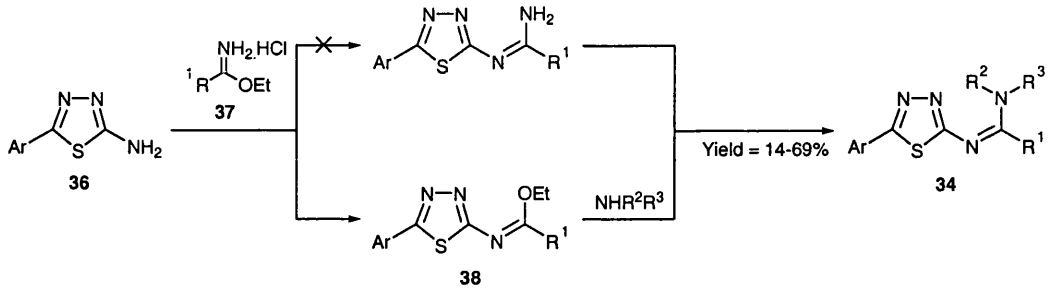
The author initially attempted the synthesis of the first two amidine compounds **33** and **34** *via* reaction of a 2-aryl-5-aminothiadiazole **36** with the hydrochloride salt of the desired imino ether **37**.[27, 28] (Scheme 1.5.2.)



36 37 34

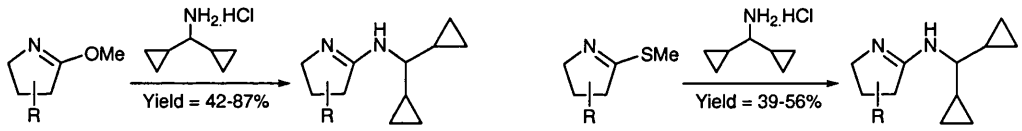
**Scheme 1.5.2.** Chapleo's proposed synthesis.

However, the substitution products formed were actually those derived from a transimidation reaction, involving amino substitution of the imino group of **37** and not replacement of its ethoxy substituent. Fortunately, this intermediate proved to be an even more valuable synthetic intermediate, since a subsequent treatment of **38** with a secondary amine enabled access to the desired amidine **34**. (Scheme 1.5.3.)




**Scheme 1.5.3.** Synthesis of amidino thiadiazoles.

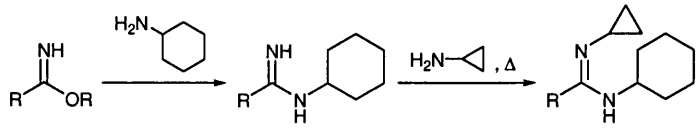
In 2001 Ehrhardt *et al.* prepared a series of 8 amidines *via* addition of amines to butyrolactim **39** and butyrothiolactim ethers **40** as analogues of clonidine,[29] which is an antihypertensive drug known to act within the central nervous system. Ehrhardt's hope was to develop new compounds with selectivity for $I_1$ imidazolidinone receptors over adenoreceptors *via* the synthesis of a series of pyrrolinic isosteres of rilmenidine, a second generation analogue of clonidine. This was achieved *via* treatment of a series of butyrolactim **39** and thiobutyrolactim ethers **40** with dicyclopropanamine, to afford a small library of amidines for screening. (Scheme 1.5.4.)




**Scheme 1.5.4.** Synthesis of a series of amidine derivatives of rilmenidine.

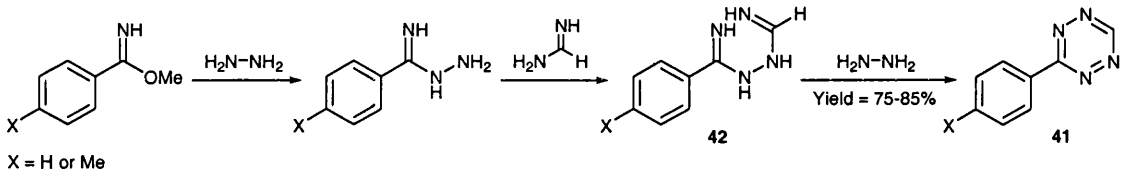
If excess amine is employed and the reaction mixture heated for prolonged reaction periods then the *N,N'*-disubstituted amidine product is formed. Interestingly, given the different reaction conditions required for substitution of the alkyloxy substituents of

imino ethers, this approach provides an excellent route to the synthesis of unsymmetrical *N,N'*-disubstituted amidines. (Scheme 1.5.5.)



**Scheme 1.5.5.** Unsymmetrical amidine formation from an imino ether.

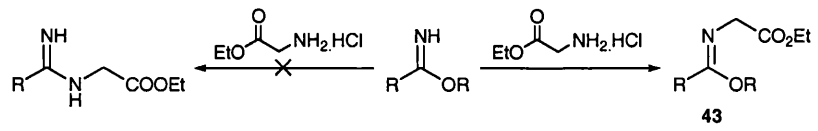
Indeed, this attractive approach has been employed for the synthesis of diverse amidines by Meresz and Foster-Verner,[30] who developed a synthetic route to unsymmetrical 3-alkyl-1,2,4,5-tetrazines **41** from intermediary *bis-N*-amino amidines **42**. Therefore, reaction of an imino ether with hydrazine, followed by reaction with a second equivalent of amidine afforded *bis*-amidine **42** that was reacted with a further equivalent of hydrazine to afford an unsymmetrical tetrazine **41** in good yield. (Scheme 1.5.6.)



**Scheme 1.5.6.** Formation of an unsymmetrical 1,2,4,5-tetrazine **41** from the corresponding imino ether and hydrazine.

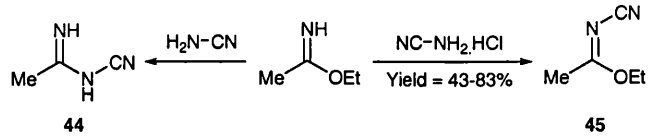
## 1.5.2. Formation of *N*-substituted imino ethers

When imino ethers react with amines under acidic conditions the imino ether undergoes an imino substitution or transimidation reaction to afford an *N*-substituted imino ether **43**. (Scheme 1.5.7.)



**Scheme 1.5.7.** Formation of *N*-substituted imino ether **43**.

Huffman and Schaefer were the first to report in 1963, that imino ethers react through their imidic centres with ensuing loss of their alkyloxy fragments to afford amidines **44**, while their imino ether hydrochloride salts reacted with substitution of the imidic nitrogen atom *via* a transimidation pathway to afford *N*-substituted imino ethers **45**.[31, 32] (Scheme 1.5.8.)



**Scheme 1.5.8.** Competing amidine formation versus transimidation.

Meyers *et al.* employed this type of reaction for the formation of substituted oxazole fragments during their stereoselective syntheses of griseoviridin and madumycin,[28] two streptogramin antibiotics isolated from the soil microorganism *Streptomyces graminofaciens*.[33] (Figure 1.5.3.)

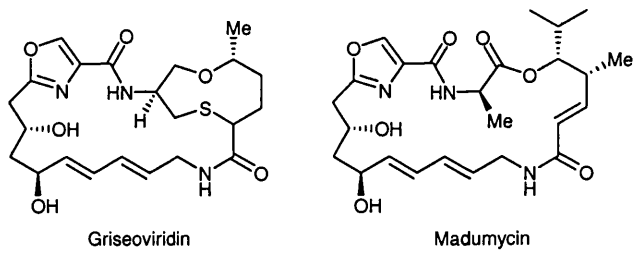
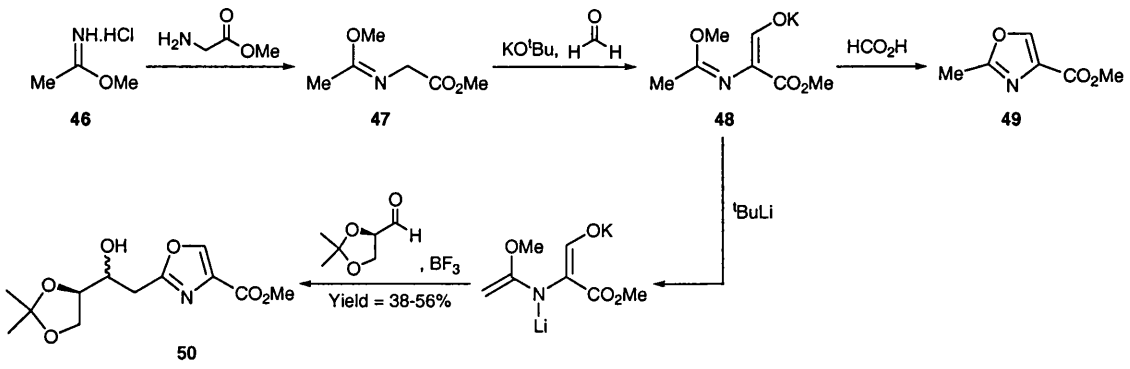


**Figure 1.5.3.** Structures of griseoviridin and madumycin.

They reacted methyl acetimidate hydrochloride **46** with glycine methyl ester to generate an imino ether **47**, which they then deprotonated using potassium *tert*-butoxide and quenched with formaldehyde to form Cornforth's intermediate **48**,[34] that cyclised on

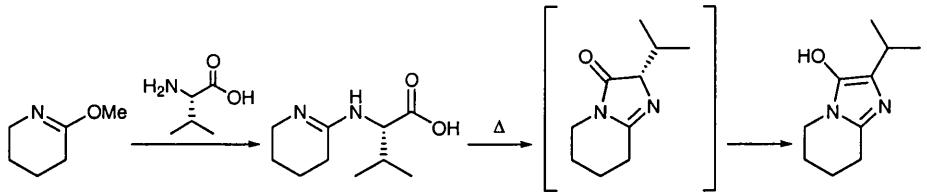
heating to afford oxazole **49**. The Cornforth intermediate **48** could also be treated with $^{t}$BuLi to effect a second deprotonation at the methyl terminus, and this acyclic *aza*-enolate was then alkylated with (*R*)-glyceraldehyde acetonide prior to formation of oxazole **50**. (Scheme 1.5.9.)




**Scheme 1.5.9.** Meyers' approach to formation of oxazoles **49** and **50**.

## 1.5.3. Reaction with amino acids and their derivatives

Imino ethers react readily with amino acids and their derivatives *via* a number of pathways.[35, 36] The simplest reaction occurs between a lactim ether and the nitrogen atom of the amino acid, resulting in formation of a substituted amidino acid, however the resultant intermediates often undergo further cyclisation reactions to generate fused dihydropyrimidinones or imidazolinones. (Scheme 1.5.10.)

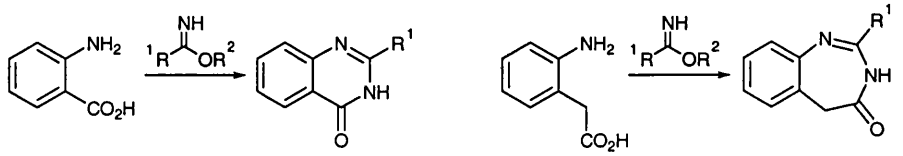



**Scheme 1.5.10.** Reaction of valerolactim ether with L-valine.

While the initial amidine formation step proceeds readily, due to the increased stability of the amidine moiety, the cyclisation step often requires harsh conditions. Körösi studied the mechanism of this reaction in 1964 and proposed that the initial step is

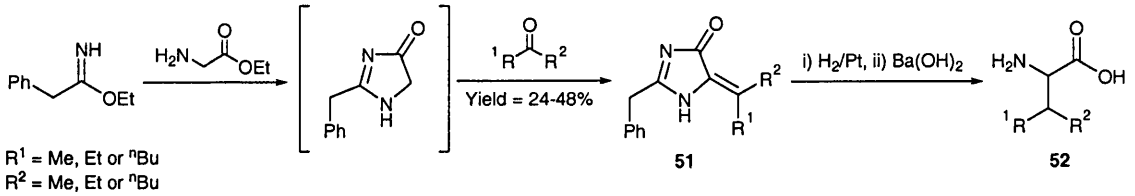
proton transfer from the amino acid to the nitrogen atom of the lactim ether,[37] which has the effect of increasing the electrophilic nature of the imidic carbon atom towards nucleophilic attack by the nitrogen atom of the amino acid. Amino esters react analogously to amino acids with lactim and imino ethers, however they do so under milder conditions.[38]

Lactim ethers react with most classes of amino acid, with the use of β, γ, δ and ε amino acids having been reported.[35] β-amino acid derivatives have also been reported to cyclise, but only where the intermediary amidino acid adopts a conformation that facilitates the cyclisation step. For example, both anthranilic and *o*-aminophenylacetic acid derivatives readily cyclise on account of the fact that the amine group is directed by virtue of the conformation imposed by the aromatic ring.[38] (Scheme 1.5.11.)




**Scheme 1.5.11.** Reaction of an imino ether with anthranilic acid or *o*-aminophenylacetic acid.

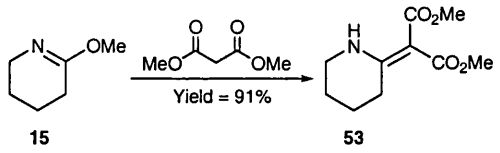
Lehr *et al.* proposed a protocol in 1953 in which imino ethers could be used to produce α-amino acids derivatives.[39] They noted that when imino ethers were allowed to react with an amino ester in a ketonic solvent, an ylidene derivative **51** was obtained. Hydrogenation of the imidazolone product using a platinum catalyst, followed by alkaline hydrolysis with barium hydroxide yielded a substituted glycine derivative **52**, containing two new stereocentres. (Scheme 1.5.12.)




**Scheme 1.5.12.** Imino ethers for the synthesis of α-amino acids **52**.

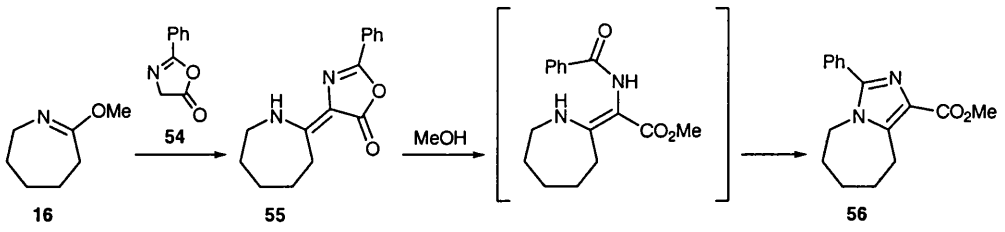
## 1.5.4. Addition of stabilised enolates to lactim ethers

The lability of the imino ether functionality allows it to react with many potential nucleophiles; with many useful examples having been reported using stabilised enolate equivalents. For example, dimethyl malonate attacks valerolactim ether **15** with displacement of the alkyloxy group resulting in formation of a stabilised enamine adduct **53** in quantitative conversion and high selectivity. This reaction is a powerful carbon-carbon bond forming reaction given the possibilities it affords for further derivitisation. (Scheme 1.5.13.)




**Scheme 1.5.13.** Reaction of valerolactim ether **15** with diethyl malonate.

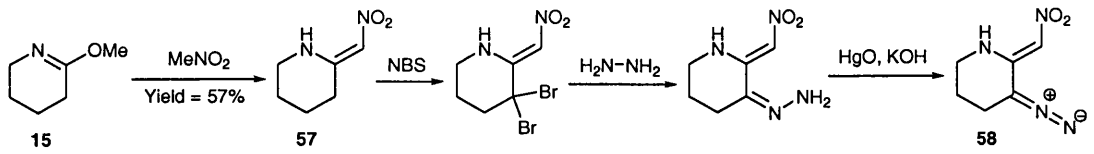
The enamine fragment of **53** may react further with other reactants, thus affording a facile route to a large range of heterocyclic compounds. In 1960 Glushkov demonstrated the potential of this approach *via* the reaction of caprolactim ether **16** with 2-phenyloxazolin-5-one **54**,[13] which afforded an enamine product **55**, that cyclised in methanol to afford the imidazole ring system **56**. (Scheme 1.5.14.)




**Scheme 1.5.14.** Reaction of phenyloxazolin-5-one **54** with caprolactim ether **16**.

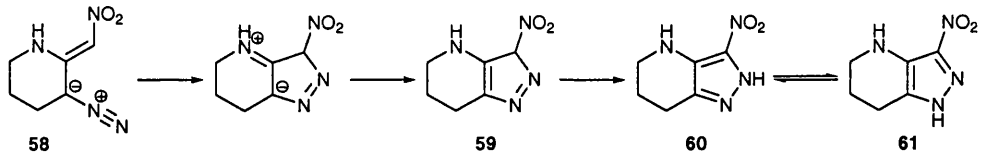
In 2000 Mete *et al.* showed that lactim ethers also reacted with nitromethane during their work on the formation of diazocompounds.[40] They reported that heating methyl valerolactim ether **15** and nitromethane at 100 °C for 18 hours with removal of methanol resulted in the desired 2-nitromethylenepiperidine **57** in moderate yield. The

group then formed the diazo compound **58** *via bis*-bromination with NBS and imine formation with hydrazine, followed by *diazo*-formation *via* oxidation with mercuric oxide. (Scheme 1.5.15.)




**Scheme 1.5.15.** Formation of a diazo piperidine **58** *via* the reaction of nitromethane with valerolactim ether **15**.

They found that the resultant 3-diazo-2-nitromethylene-piperidine **58** underwent slow rearrangement to its pyrazolo-tetrahydropyridine derivative **59**, which in turn was found to be in equilibrium with two different tautomeric forms **60** and **61**. (Scheme 1.5.16.)

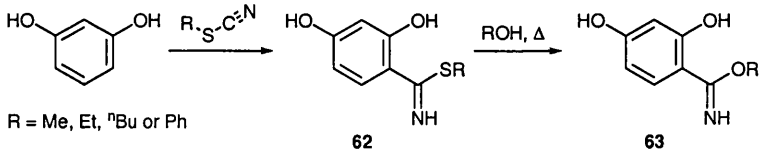



**Scheme 1.5.16.** Cyclisation and rearrangement of 3-diazo-2-nitromethylene-piperidine **58**.

## 1.5.5. Alkyloxy substitution

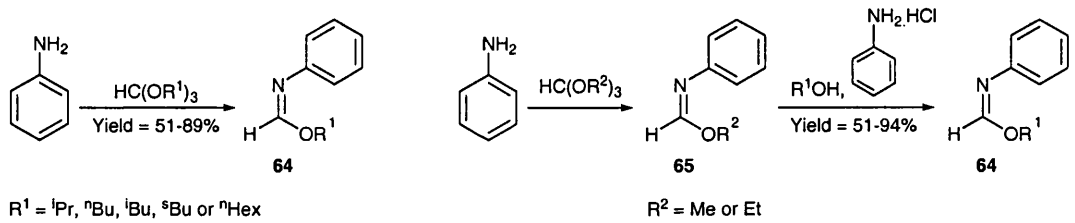
It is well known that lactim ethers readily undergo alkyloxy substitution reactions with alcohols enabling facile access to a wide range of lactim ethers.[41] It has been reported that simple heating with a higher boiling alcohol results in alkyloxy substitution by removal of the lower boiling alcohol *via* distillation.[42, 43] It is worthy of note that the most reliable routes to imino ethers using this approach employ imino ether substrates derived from low molecular weight alcohols such as methanol and ethanol.[38]

In 1923 Kaufmann and Adams reported that thioimino ethers of resorcinol **62** underwent a transesterification type reaction to afford aryl oxy-imino ethers **63** *via* heating to reflux with an alcohol.[43] (Scheme 1.5.17.)



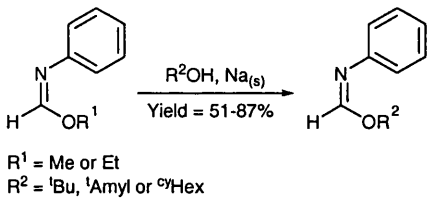

**Scheme 1.5.17.** Substitution of a thioimino ether derivative of resorcinol **62** to afford an imino ether **63**.

It was reported by Roberts *et al.* in 1955 that the presence of acid has a positive effect on the yield of this type of transesterification reaction.[42] They were investigating direct reaction of aniline with a range of alkyl orthoformates in an effort to prepare the corresponding *N*-phenyl formimidate ethers **64**. However, it was found that an indirect approach involving formation of the imino ether **65** using methyl or ethyl orthoformate, followed by transesterification with an alcohol led to higher yields of this class of compound. (Scheme 1.5.18.)



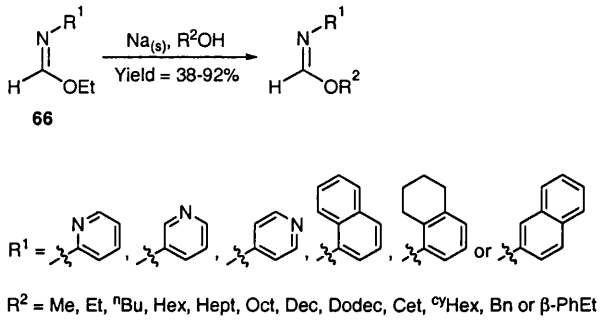

**Scheme 1.5.18.** Roberts' formation of *N*-phenyl formimidate ethers **65** followed by transesterification under acidic conditions.

The group developed a second synthetic route in order to combat the problems associated with preparing imino ethers containing alkyloxy fragments prone to dehydration. They reported that generation of sodium alkoxides of hindered alcohols was successful in promoting nucleophilic attack at the imidic centre of imino ethers. (Scheme 1.5.19.)



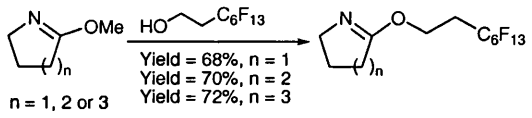

**Scheme 1.5.19.** Base catalysed transimidation of *N*-phenyl formimidate ethers.

Benkó and Pallos published work 16 years later detailing further research on transesterification of methyl and ethyl *N*-pyridyl formimidate ethers **66**.[41, 44] They reported that the reaction was best carried out using sodium alkoxides, with poorer yields being reported using acid catalysts.[41] (Scheme 1.5.20.)




**Scheme 1.5.20.** Benkó and Pallos' base catalysed transesterification reactions of *N*-aryl formimidate ethers **66**.

In 1994 Brace *et al.* carried out alkyloxy substitution reactions on a range of 5, 6 and 7 membered lactim ethers using polyfluorinated alcohols as nucleophiles in moderate to good yield.[45] (Scheme 1.5.21.)




**Scheme 1.5.21.** Brace's synthesis of polyfluorinated lactim ethers.

Yang *et al.* employed an intramolecular lactim ether bond forming reaction in 1994 during their synthesis of azithromycin, in the first reported synthesis of the *aza*lide

antibiotics.[46] Azithromycin differs from erythromycin A by the incorporation of an extra *N*-methyl substituent at the 9a position of the lactone, increasing the ring size from a fourteen to a fifteen membered macrocycle. This subtle variation increased potency against gram-negative bacteria by improving its bioavailability. (Figure 1.5.4.)

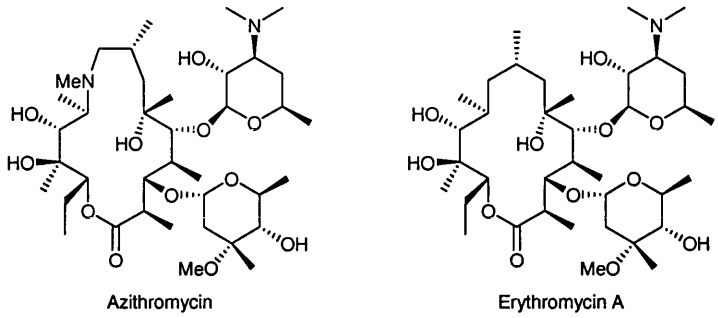
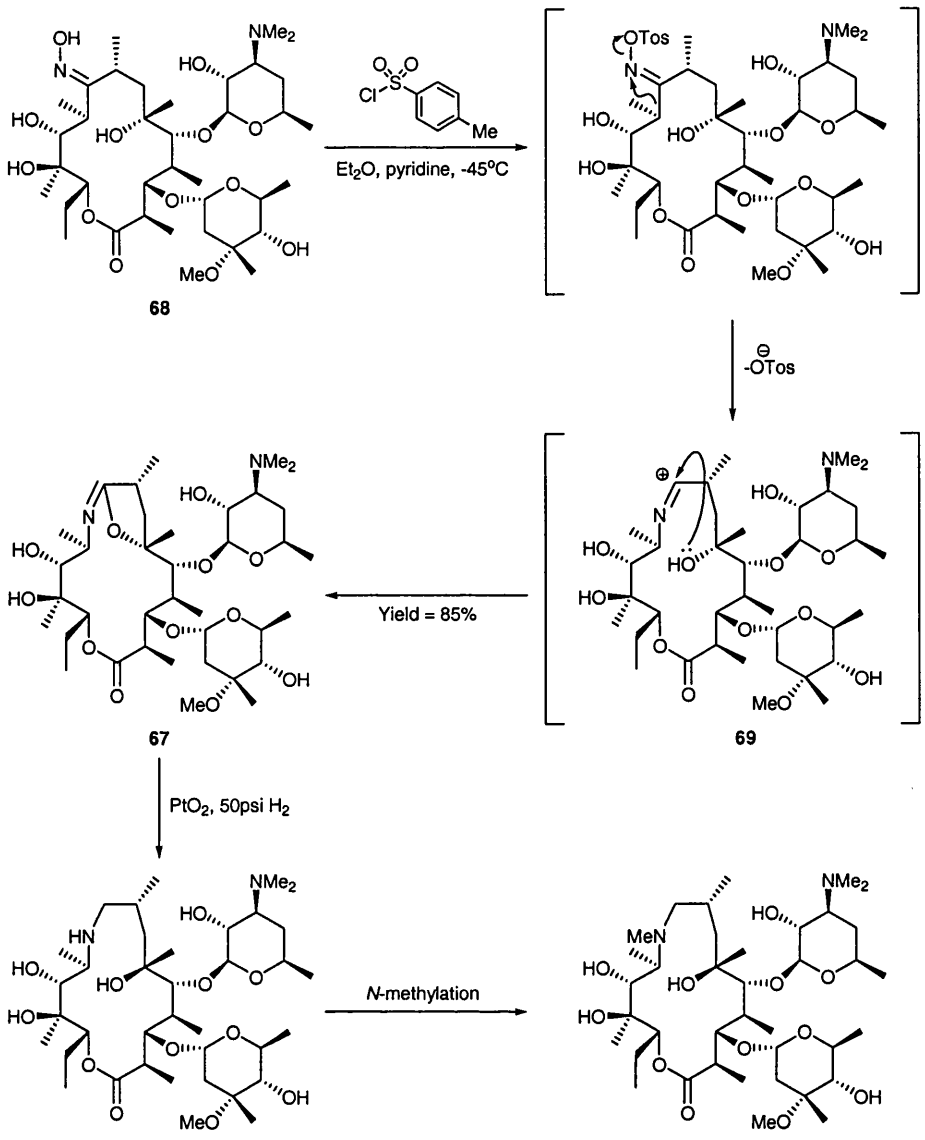



**Figure 1.5.4.** Structures of azithromycin and erythromycin A.

A 6,9-imino ether intermediate **67** was generated by Beckmann rearrangement of 9(*E*)-oxime erythromycin **68** at 0 °C in aqueous acetone, employing toluenesulfonyl chloride to activate the oxime oxygen to migration, with intramolecular quenching of the intermediate nitrilium cation **69** by an adjacent hydroxyl group. Subsequent hydrogenation of **67** at high pressure followed by *N*-methylation furnished the desired azithromycin. (Scheme 1.5.22.)




**Scheme 1.5.22.** Yang's synthesis of azithromycin.

Yang *et al.* isolated a second 9,11-stable imino ether intermediate **70** at lower temperature (-45 °C) formed from intramolecular trapping of the nitrilium cation **69** with another hydroxyl group. It was also reported that the 6,9 imino ether **67** readily isomerised in a range of organic solvents *via* a transesterification mechanism to afford the 9,11 imino ether **70**. (Figure 1.5.5.)

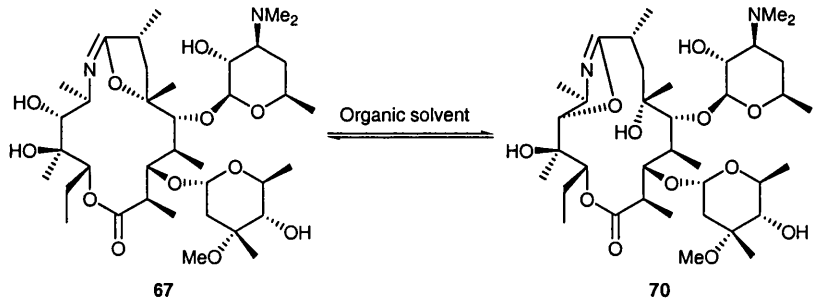
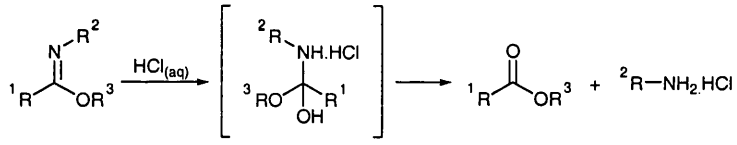



**Figure 1.5.5.** Structure of the 6,9-imino ether **67** and 9,11-imino ether **70** interconvert readily in organic solvents.

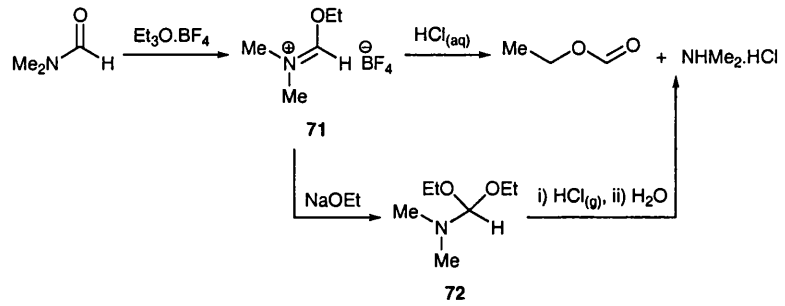
## 1.5.6. Hydrolysis of imino ethers and lactim ethers

Imino ethers are readily hydrolysed in the presence of catalytic amounts of acid to provide the corresponding amine (often as the ammonium salt) and ester in good yield.[24, 47-50] This type of hydrolysis reaction has been widely studied since it is considered to be a good model for the unstable tetrahedral intermediate of acyl transfer reactions. (Scheme 1.5.23.)



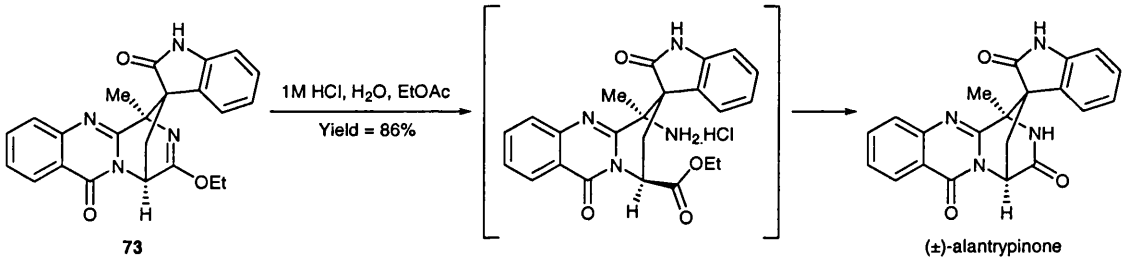

**Scheme 1.5.23.** Acid catalysed hydrolysis of an imino ether.

Meerwein *et al.* reported on imino ether hydrolysis in 1961 during their research into the development of trialkyloxonium tetrafluoroboronates for amide *O*-alkylation reactions.[20] They successfully reacted DMF with triethyloxonium tetrafluoroboronate to generate the corresponding imino ether tetrafluoroboronate salt **71**, which they then treated with sodium ethoxide to afford a dimethylaminoformamide diethyl acetal **72**. Both these compounds were then hydrolysed to afford ethyl formate and dimethyl ammonium chloride *via* treatment with HCl and water. (Scheme 1.5.24.)



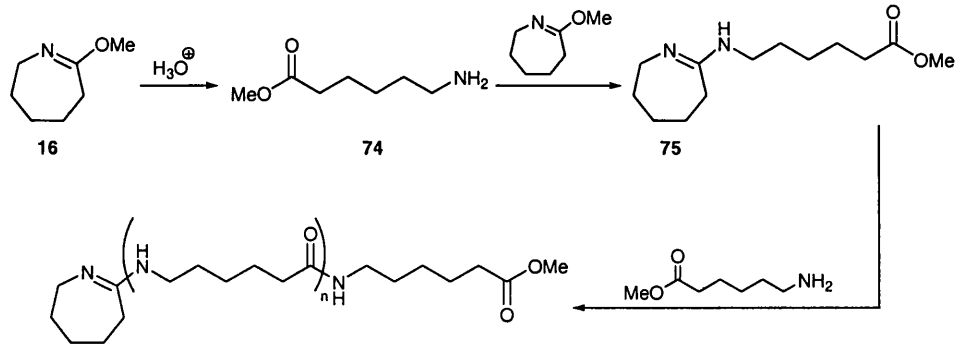

**Scheme 1.5.24.** Meerwein's original hydrolysis studies on imino ethers.

Lactim ethers also decompose under mild acidic aqueous conditions, to yield their corresponding ω-amino esters, as their hydrochloride salts, which on neutralisation afforded the corresponding lactam. (Scheme 1.5.25.) This was demonstrated by Kende *et al.* during their synthesis of (±)-alantrypinone, a novel penicillium alkaloid.[51]



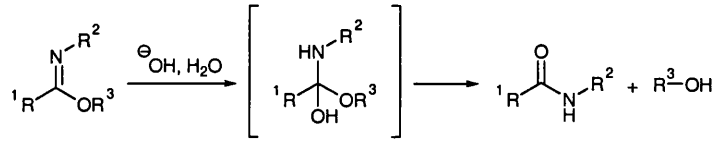

**Scheme 1.5.25.** Acid catalysed hydrolysis of a lactim ether **73** followed by intramolecular cyclisation to afford (±)-alantrypinone.

Körösi showed that treatment of caprolactim ether **16** with water and heating resulted in formation of the corresponding amino ester **74**,[37] although in the same report he showed that extended heating resulted in polymerisation. Körösi suggested a mechanism for the formation of the polymeric material that proceeded *via* an amidine intermediate **75**. (Scheme 1.5.26.)



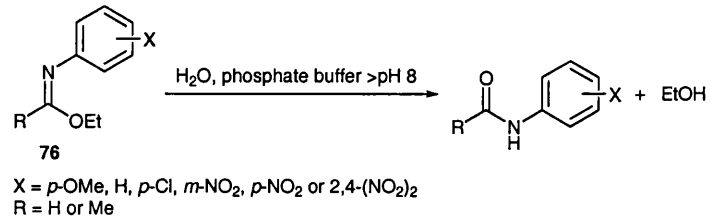
**Scheme 1.5.26.** Körösi hydrolysis and polymerisation of caprolactim ether **16**.

Imino ethers have also been shown to undergo hydrolysis under basic conditions to afford their corresponding amides. Under these conditions the leaving properties of the amine are reduced, thus allowing the ester group to become the leaving group, affording the corresponding amide and alcohol.[47, 49, 50, 52-54] (Scheme 1.5.27.)



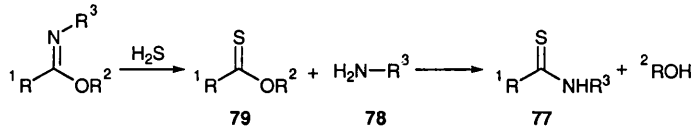
**Scheme 1.5.27.** Hydrolysis of an imino ether under basic conditions.

In 1973 Schmir *et al.* reported an in depth kinetic study of the hydrolysis of a range of *N*-aryl imino ethers **76** under basic conditions.[48] They reported that as the pH of the buffer solution rose then the yield of the amide product increased, with the amide product being afforded in quantitative yields at pH > 10. (Scheme 1.5.28.)



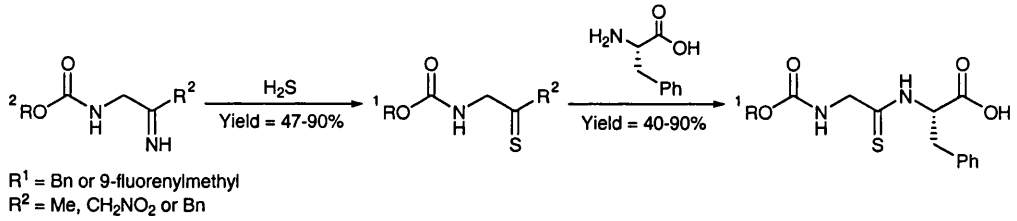
**Scheme 1.5.28.** Basic hydrolysis of *N*-aryl imino ethers **76**.

Employment of $H_2S$ as a nucleophile gives rise to the formation of thioesters, although this reaction does not proceed as readily as the corresponding hydrolysis reaction with water. The most commonly observed side product in these reactions is formation of the corresponding thioamide **77** as a result of a reaction involving secondary attack of the amine **78** on the thioester **79**. (Scheme 1.5.29.)




**Scheme 1.5.29.** Formation of thioester **79** from an imino ether.

During the late eighties there was a tremendous growth of interest in the preparation of thiopeptides with particular attention being placed on the selective formation of thioamide groups within a peptide backbone.[55, 56] In this regard, Williams *et al.* synthesised an array of methyl, ethyl and benzyl thioesters from imino ethers in 1988, and employed them to thioacylate amino acids, peptides esters or amide derivatives.[57] (Scheme 1.5.30.)




**Scheme 1.5.30.** Selective thiopeptide formation using Z- and Fmoc-glycine derived imino ethers.

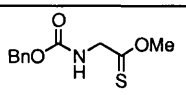
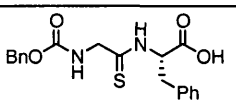
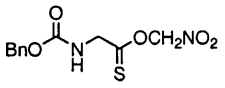
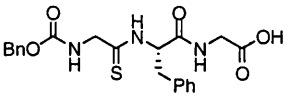
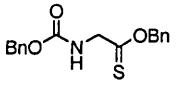
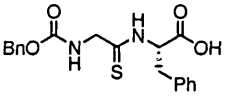
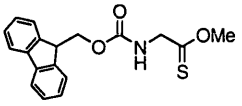
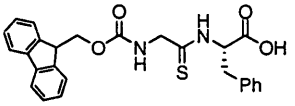
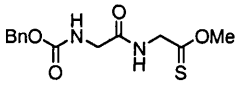
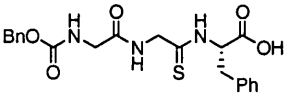
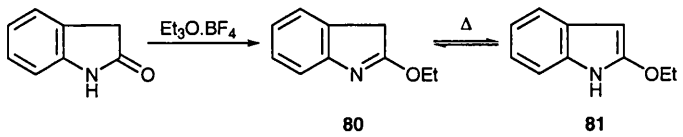
| Entry | Thioester formed | % yield | Thiopeptide formed | % yield |
|---|---|---|---|---|
| 1 |  | 92 |  | 82 |
| 2 |  | 47 |  | 40 |
| 3 |  | 90 |  | 78 |
| 4 |  | 89 |  | 55 |
| 5 |  | 90 |  | 90 |

**Table 1.5.1.**

## 1.5.7. Tautomerisation

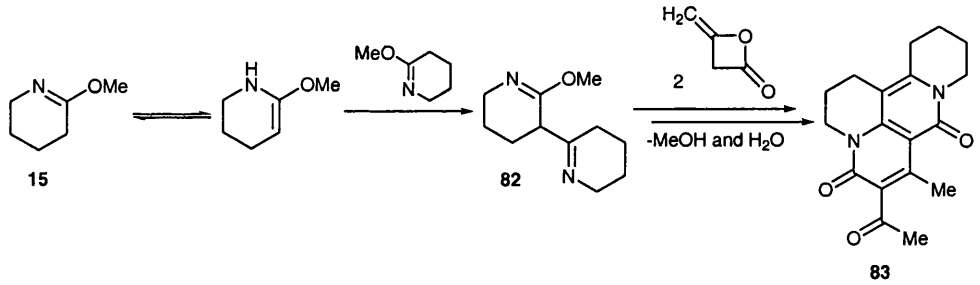
Carbonyls possessing an α-proton can readily undergo tautomerisation to their enolic form and imino ethers also undergo such tautomerisation, particularly in the presence of functionality that can result in stabilisation of the enamine tautomer *via* conjugation. In 1964 Harley-Mason and Leeney demonstrated that certain imino ethers exist in equilibrium with their enamine tautomer.[58] They treated a range of oxindole derivatives with Meerwein's reagent to give the expected lactim ether product **80** which on heating to its sublimation point afforded the enamine tautomer **81**, which was found to be stable as a result of conjugation with the neighbouring aromatic ring. Reversion to its imino ether form **80** was achieved by heating the enamine tautomer above its new melting point. (Scheme 1.5.31.)




80 81

**Scheme 1.5.31.** Tautomerisation between the imino ether **80** and enamine **81** forms of an oxindole.

Kato *et al.* showed in 1975 that lactim ethers could dimerise *via* reaction through their enamine tautomer, with the enamine carbon atom acting as a nucleophile.[59] The reaction proceeds with subsequent loss of methanol to afford the dimer **82**. They then reacted the dimer with two equivalents of diketene to afford a highly functionalised tetracyclic heterocycle **83**. (Scheme 1.5.32.)

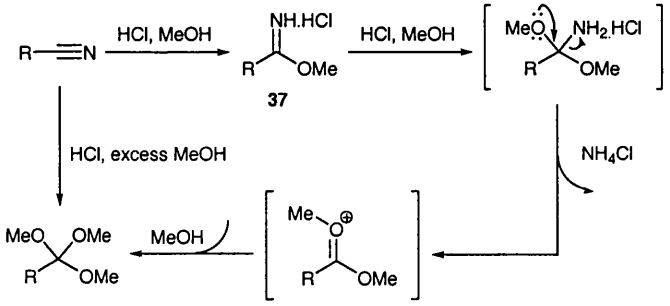



15 82 83

**Scheme 1.5.32.** Tautomerisation of valerolactim ether **15** and ensuing dimerisation.

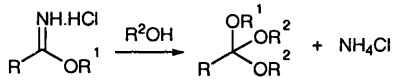
## 1.5.8. Triortho ester formation

Imino ethers can react with alcohols at room temperature under strongly acidic conditions to afford simple or mixed ortho esters.[60, 61] This reaction was first noticed from observations on the Pinner synthesis where forcing conditions result in attack of excess alcohol on the imino ether hydrochloride intermediate **37**, with subsequent release of the nitrogen atom as its ammonium salt.[1] (Scheme 1.5.33.)




**Scheme 1.5.33.** Pinner synthesis of ortho esters.

This transformation occurs as a side reaction of the Pinner synthesis and was originally characterised by poor yields and slow reaction rates, however work performed during the late 1940's and 1950's by McElvain and co-workers succeeded in optimising it as a viable approach for the synthesis of trialkyl ortho esters. They discovered that refluxing imino ether salts in the presence of a large excess of alcohol,[62] or stirring with alcohol in petrol at room temperature[63-65] gave improved yields of the desired ortho ester. (Scheme 1.5.34.)




**Scheme 1.5.34.** Generic overview for the formation of triortho esters.

There are several competing side reactions that must be considered if good yields of ortho esters are to be achieved; i) heating allows imino ethers to undergo the Chapman rearrangement to their corresponding to their *N*-alkyl amides, thus any reaction involving high temperatures must be carefully monitored; ii) the reaction mixture must be free from excess acid, as the formed triortho ester can easily degrade to its corresponding ester, alcohol and alkyl halide; iii) the reaction mixture must be performed under anhydrous conditions as the triortho ester can undergo rapid hydrolysis to the ester and alcohol.

During the late 1980's and early 1990's Kelley *et al.* synthesised 78U79, a purine based anticonvulsant drug.[66] It was noted however that compounds containing this purine rings system exhibited a propensity to cause emesis, and as a consequence structure

activity optimisation studies carried out in order to eliminate these side effects. In 1995 Kelley *et al.* prepared a series of triortho esters from the intermediary imino ether salts **84** during their synthesis of eleven pyrazines as test compounds for anticonvulsant activity,[67] with the 1,2,4-triazolo[4,3-*a*]pyrazine ring system of **85** serving as bioisosteres of the purine fragment of 78U79. (Figure 1.5.35.)

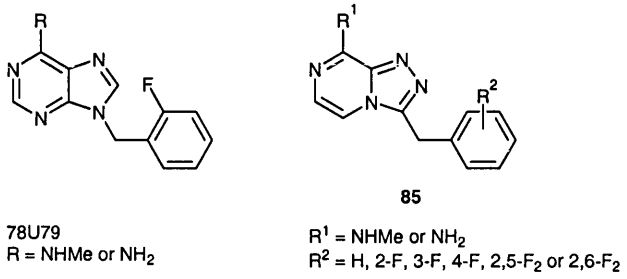
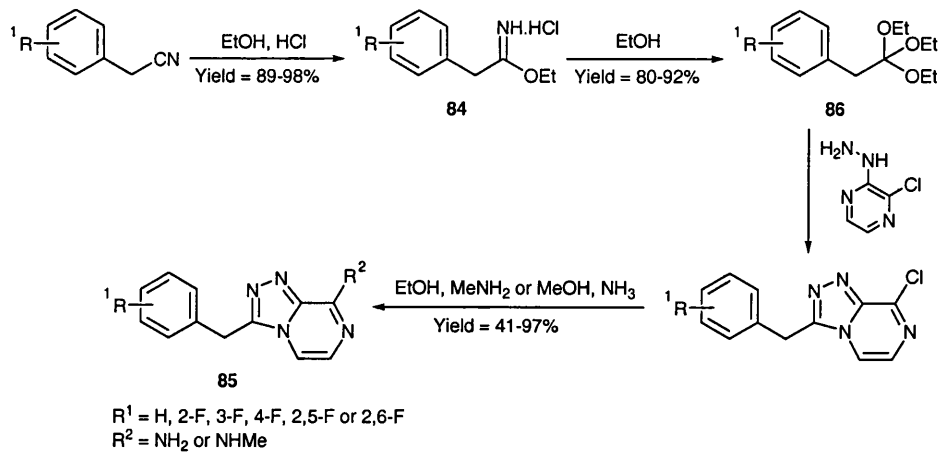



**Figure 1.5.35.** 78U79 and the generic pyrazines **85** used by Kelley.

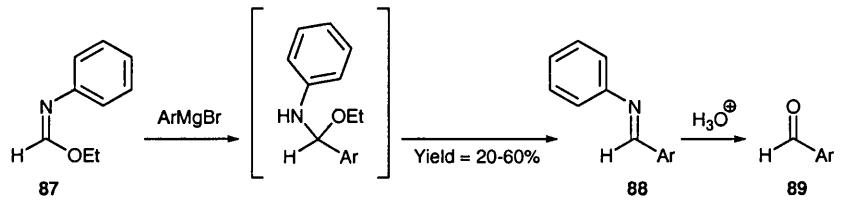
The author's work centred on developing a simple four stage synthetic protocol starting from the corresponding phenyl acetonitriles, that were converted to their triethyl ortho esters **86** in high overall yields, *via* treatment of an intermediate imino ether hydrochloride salt **84** with a large excess of ethanol. Subsequent treatment of these ortho esters with hydrazines afforded the triazolopyrazine cores **85**, a number of which displayed high anticonvulsant activity, without the side effects of the purine analogue. (Scheme 1.5.36.)




**Scheme 1.5.36.** Use of triortho esters **86** in the synthesis of a range of pyrazines **85**.

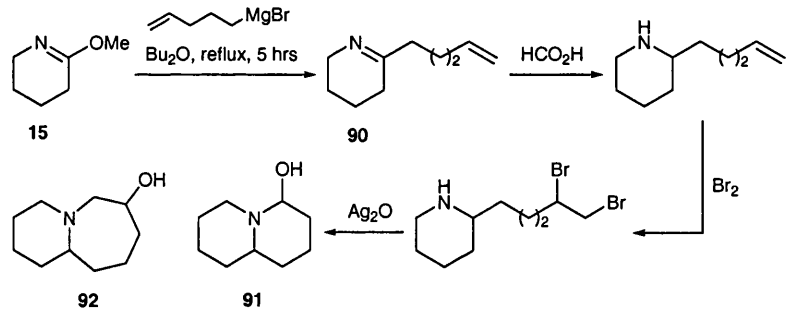
## 1.5.9. Reaction with organometallic reagents

Imino ethers have often been shown to undergo nucleophilic attack by organometallic reagents such as Grignard reagents and alkyl lithiums.[23, 68-70] The reaction proceeds with substitution of the alkyloxy group for an alkyl group of the organometallic reagent used, affording the corresponding imine, with excess nucleophile often resulting in the formation of a tertiary amine. This nucleophilic addition reaction was first demonstrated as early as 1941 when Smith and Nichols reacted a series of aryl Grignard reagents with ethyl *N*-phenyl formimidate **87** to generate the corresponding imines **88**, which were then hydrolysed to the resultant aryl aldehydes **89**.[71] (Scheme 1.5.37.)



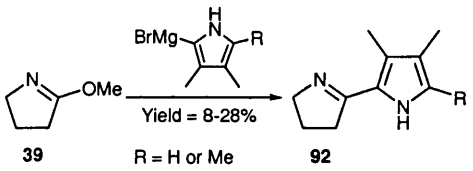

**Scheme 1.5.37.** Reaction of an imino ether **87** with aryl Grignard reagents and subsequent hydrolysis.

In 1959 Lukeš and Červinka showed that lactim ethers are also susceptible to nucleophilic attack when they reacted pent-4-enyl magnesium bromide with valerolactim ether **15**,[72] to form a pentenyl-tetrahydropyridine **90** in moderate yield. The product was subsequently elaborated to afford the desired 4-hydroxymethylquinolizidone **91**, as well as 1-*aza*bicyclo-[0,4,5]-undecan-3-ol **92**. (Scheme 1.5.38.)



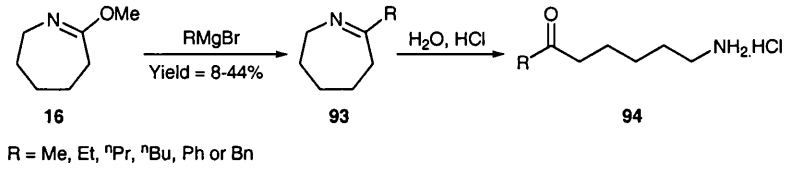

**Scheme 1.5.38.** Červinka and Lukeš synthesis of 4-hydroxymethylquinolizidone **91** from valerolactim ether **15**.

Further work carried out by Booth, Johnson and Johnson three years later demonstrated that reaction of butyrolactim ether **39** with the Grignard reagents of 2,3,4-trimethylpyrrole and 3,4-dimethyl pyrrole resulted in 2,2'-pyrrylpyrrolines **92**,[69] however the yields obtained were generally low. (Scheme 1.5.39.)



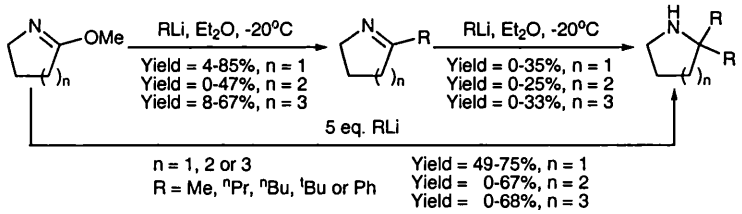

**Scheme 1.5.39.** Reaction of butyrolactim ether **39** with pyrrole derived Grignard reagents.

This work was followed by more general work on the reaction of Grignard reagents with lactim ethers by Dudek and Li-Kuan.[68] Their work centred on the synthesis of cyclic 2-alkyl imines from caprolactim ether **16** *via* reaction with alkyl magnesium bromides affording a series of imines **93** in 8 to 44% yield. The pair then hydrolysed these cyclic imines to produce a range of ω-amino carbonyl compounds **94**. (Scheme 1.5.40.)



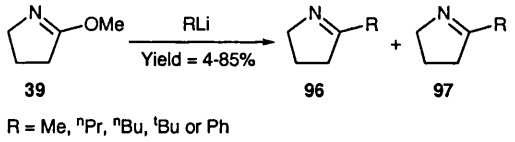

**Scheme 1.5.40.** Reaction of caprolactim ether with Grignard reagents to afford an ω-amino ketone **94**.

Smith *et al.* performed the widest and most comprehensive study on the reaction of the organolithiums with lactim ethers in 1984.[73] They studied reaction of a large range of organolithium reagents with butyro, valero and caprolactim ethers, concentrating on formation of the corresponding imines and amines as building blocks for indolizidines and quinolizidines. They noted that while addition of organolithium reagents to lactim ethers gave moderate to good yields of imines using butyrolactim ether (60 to 85% unpurified), yields of imine dropped off dramatically for valero and caprolactim ethers (0 to 50%). (Scheme 1.5.41.)




**Scheme 1.5.41.** Reaction of organolithiums with lactim ethers.

The main problem the authors encountered was further reaction of the imine intermediate to afford 2,2-dialkyl amines, which was ascribed to the well known ability of imines to react with alkyl lithiums. For example, in the case of allyl magnesium iodide, butyrolactim ether afforded 2,2-allylpyrrolidine as the only isolatable product. The authors reported that controlled addition of a single equivalent of alkyl lithium to lactim ethers failed to afford a reliable route to 2-alkyl imines, with the reaction usually returning unreacted lactim ether **39** (typically 40 to 100%), 0-30% yield of imine **96**, with the remainder being 2,2-dialkyl amine **97**. The only notable exception was for the use of PhLi which afforded the corresponding imine in 85% yield. (Scheme 1.5.42.)



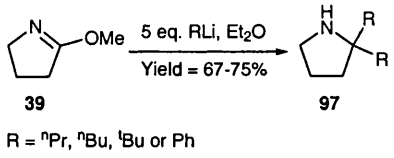

**Scheme 1.5.42.** Reaction of organolithiums with lactim ethers to form imines.

| Entry | Alkyl Lithium | % recovered starting butyrolactim ether **39** | % yield of butyroimine **96** | % yield of 2,2-dialkyl amine **97** |
|---|---|---|---|---|
| 1 | MeLi | 59 | 4 | 0 |
| 2 | $^{n}$PrLi | 52 | 11 | 35 |
| 3 | $^{n}$BuLi | 38 | 34 | 24 |
| 4 | $^{t}$BuLi | 51 | 49 | 0 |
| 5 | PhLi | 5 | 85 | 0 |

All yields unpurified.

**Table 1.5.2.**

It was noted that employment of five equivalents of organolithium afforded reliable 60-75% yields of the desired 2,2-dialkyl amines **97**, except in the case of the sterically demanding $^{t}$BuLi, which gave the corresponding di-$^{t}$butyl amine **98** in only 45% yield. (Scheme 1.5.43.)



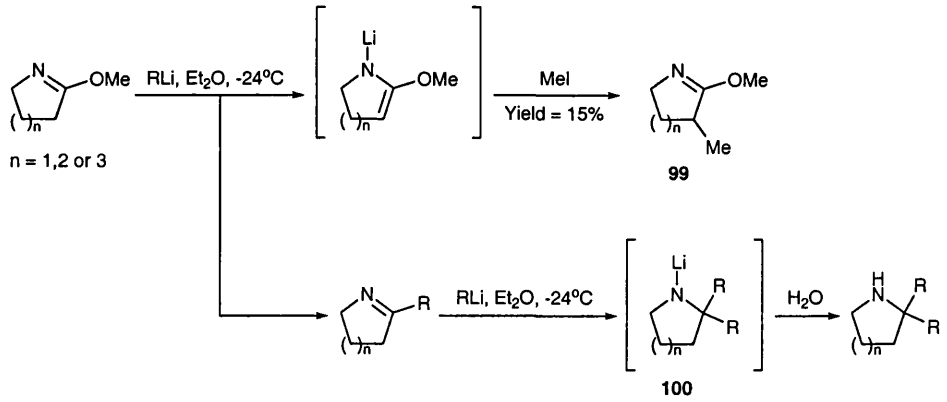

**Scheme 1.5.43.** Synthesis of 2,2-dialkylamines **97** from butyrolactim ether **39**.

| Entry | Alkyl lithium | % recovered starting butryolactim ether **39** | % yield of butyroimine **96** | % yield of 2,2-dialkyl amine **97** |
|---|---|---|---|---|
| 1 | $^{n}$PrLi | >5 | >5 | 67 |
| 2 | $^{n}$BuLi | >5 | >5 | 75 |
| 3 | $^{t}$BuLi | >5 | 13 | 49 |
| 4 | PhLi | >5 | >5 | 74 |

All yields unpurified.

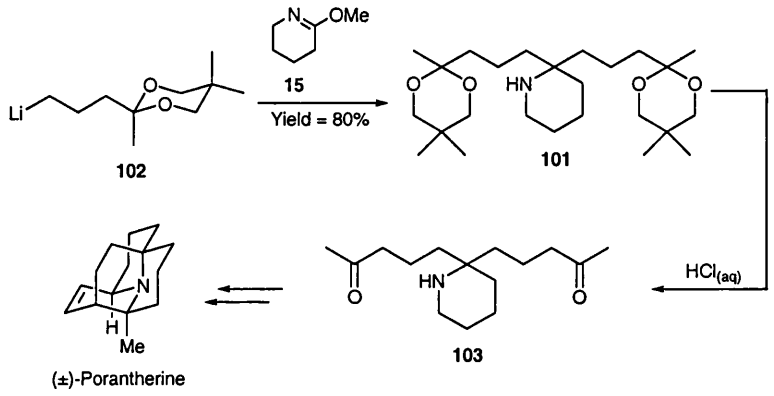
**Table 1.5.3.**

The group reported that starting material in these reactions was the result of 'a minor reaction' where the starting lactim ether was deprotonated by the organolithium to afford an *aza*-enolate intermediate. They attempted to prove this mechanism by quenching the reaction mixture with methyl iodide and found that small amounts of α-methyl butyrolactim ether **99** could be formed. Furthermore, they noted that as the basicity of the organolithium species decreased the amounts of α-alkylated material recovered became smaller, implying that the organolithium species was acting as the source of base and not the lithium 2,2-dialkyl amide species **100** generated *in situ*. The potential of this type of *aza*-enolate alkylation strategy for the synthesis of α-alkyl lactim ethers will be discussed in more detail as part of the research program described in Chapter 2 of this thesis. (Scheme 1.5.44.)




**Scheme 1.5.44.** Alkylation of the *aza*-enolate of lactim ethers using the initial organolithium as a base.

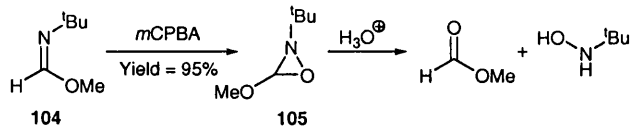
In 1986 Ryckman and Stevens reported a total synthesis of (±)-Porantherine, a major alkaloid isolated from the alkaloid rich plant *Poranthera corymbosa*,[74] that is responsible for many livestock poisonings in New South Wales and Queensland. They planned a retrosynthetic approach that required access to a key *bis*-acetal amine **101**, and performed test reactions on valerolactim ether **15** using butyl and 4-pentenyl lithium as nucleophiles to afford their corresponding 2,2-disubstituted piperidines in 72 and 85% yield. It was then found that reaction of five equivalents of valerolactim ether **15** with one equivalent of lithium ketal species **102** resulted in the desired diketoamine product **103** in 80% yield. (Scheme 1.5.45.)




**Scheme 1.5.45.** Nucleophilic attack of a *bis*-acetal lithium reagent **102** on valerolactim ether **15**.

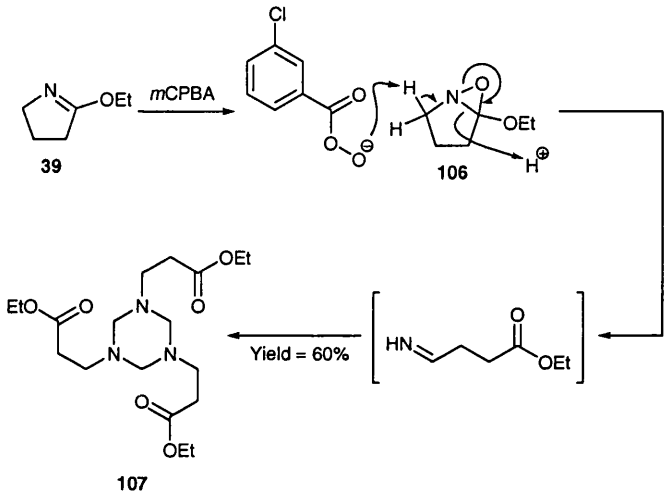
## 1.5.10. Oxidation and reduction

A relatively small number of reports on the oxidation of imino ethers have been reported to date. The most in depth oxidation study was performed by Aue *et al.* in 1973 and 1974,[75, 76] who treated a series of *N*-substituted imino ethers and lactim ethers with *m*CPBA to generate a series of oxaziranes, as potentially valuable synthetic intermediates. For the case of methyl *N*-$^t$butyl formimidate **104** the expected oxazirane **105** was formed, which on treatment with aqueous acid yielded $^t$butyl hydroxylamine and methyl formate. This approach represents a useful synthetic protocol for the synthesis of substituted hydroxylamines from formamide. (Scheme 1.5.46.)



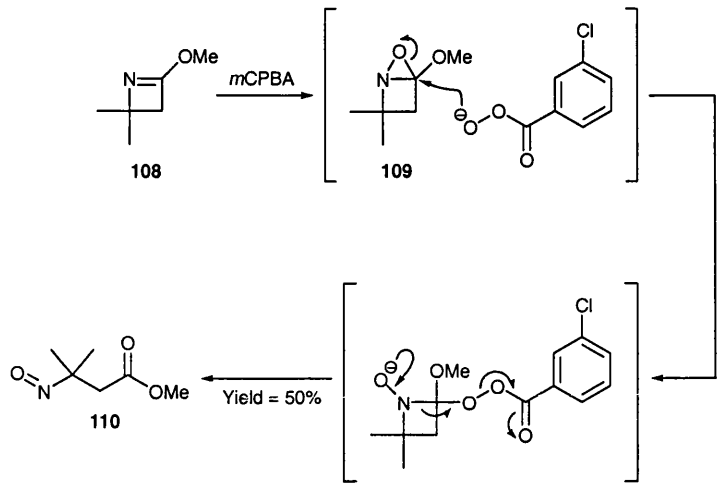

**Scheme 1.5.46.** Oxidation of an imino ether **104** to afford an oxazirane **105** and subsequent acid hydrolysis.

In the case of butyrolactim ether **39** the expected oxazirane **106** was obtained in 60% yield, however it was noted that it readily decomposed thermally in the presence of acid to afford the trimer of ethyl-4-iminobutanoate **107**. (Scheme 1.5.47.)



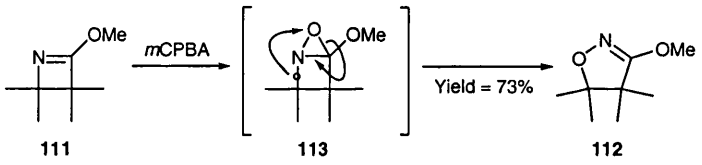

**Scheme 1.5.47.** Oxidation of butyrolactim ether **39** with *m*CPBA.

The author also studied the oxidation of a betalactim ether **108** and found NMR evidence at low temperature for the formation of 1-*aza*-5-oxabicyclo[2.1.0]pentane **109** which decomposed to the nitroso ester **110**. (Scheme 1.5.48.)



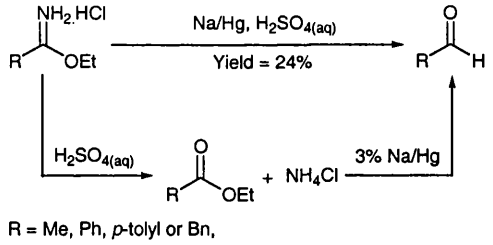

**Scheme 1.5.48.** Oxidation of a betalactim ether **108** to afford the nitroso ester **110**.

Alternatively, oxidation of tetramethyl betalactim ether **111** with *m*CPBA resulted in the formation of the alternative oxazole product **112**. It was proposed that this reaction proceeded *via* an oxazirinane intermediate **113** that subsequently rearranged to the observed oxazoline product **112**. (Scheme 1.5.49.)



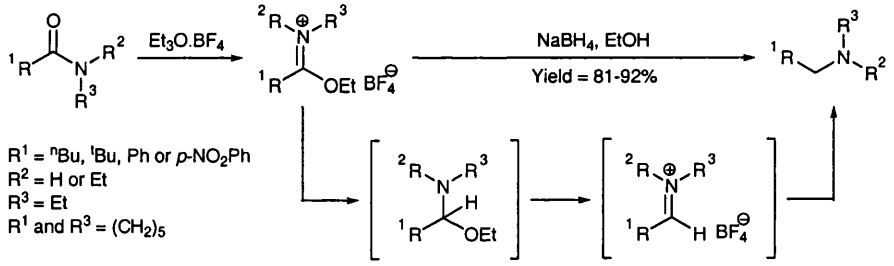

**Scheme 1.5.49.** Oxidation of tetramethyl betalactim ether **111** using *m*CPBA.

Reduction of lactim ethers on the other hand has been far more widely studied, with Henle being the first to report the reduction of simple imino ether salts in 1905.[77] His protocol involved treatment of imino ether hydrochloride salts with 3% sodium amalgam and dilute mineral acid to directly afford an aldehyde after two hours, with a yield of 24% being reported for the methyl benzimidate salt. However, given the aqueous acidic conditions used it is entirely possible that the imino ether was hydrolysed *in situ* to its ester, which in turn was reduced to an aldehyde in low yield by the sodium mercury amalgam. (Scheme 1.5.50.)




**Scheme 1.5.50.** Reduction of imino ethers using sodium mercury amalgam.

In 1968 Borch reduced a wide range of amides and lactams by converting them to their corresponding imino and lactim ethers which could then be reduced to their amines *via* treatment with sodium borohydride,[78] with the reduction step occurring in high yield for a range of cyclic and acyclic imino ethers (81 to 94%). Borch speculated on a mechanism involving initial attack of the borohydride anion at the imidic centre affording a tetrahedral intermediate that decomposes *via* expulsion of the alkyloxy fragment to afford an imine, which is then further reduced under well established precedent. (Scheme 1.5.51.)




**Scheme 1.5.51.** Borohydride reduction of an imino ether generated *in situ* from their corresponding amides.

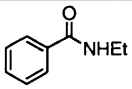
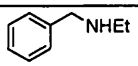
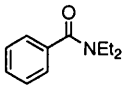
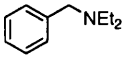
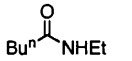
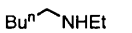
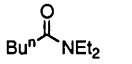
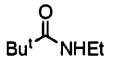
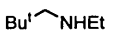
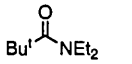
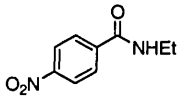
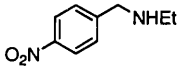
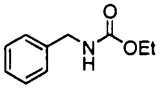
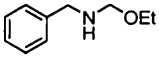
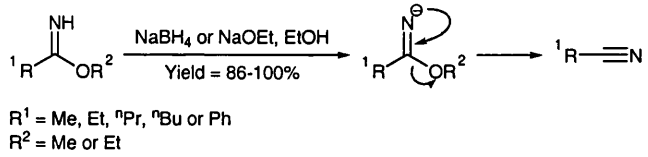
| Entry | Amide | Amine | % yield |
|---|---|---|---|
| 1 |  |  | 92 |
| 2 |  |  | 89 |
| 3 |  |  | 83 |
| 4 |  |  | 94 |
| 5 |  |  | 84 |
| 6 |  |  | 83 |
| 7 |  |  | 92 |
| 8 |  |  | 81 |
| 9 |  |  | 92 |

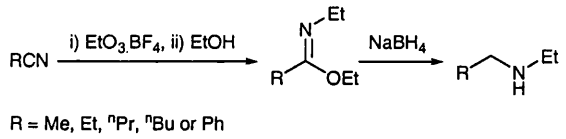
**Table 1.5.4.**

Borch also reported that reduction of primary imino ethers with sodium borohydride in ethanol did not result in primary amines, but instead gave nitriles as the major product.[78] Optimisation of this elimination reaction lead to the discovery that sodium ethoxide was an effective base for converting this class of imino ether into nitriles in good yield (86% to quantitative yield). (Scheme 1.5.52.)



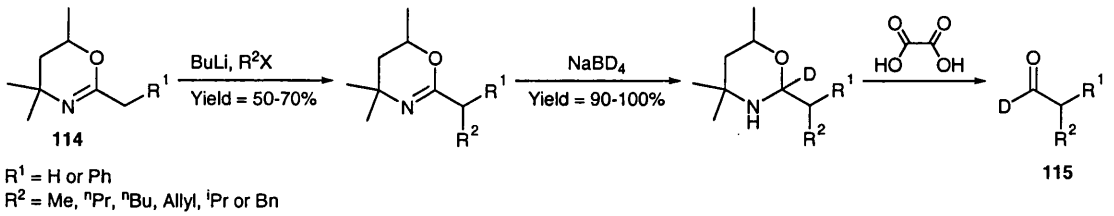

**Scheme 1.5.52.** Reduction of a primary imino ether to the corresponding cyanide.

Later in 1969 Borch devised a protocol that enabled nitriles to be reduced by sodium borohydride to their corresponding amines in high yields *via* formation of an intermediate imino ether,[79] as an alternative to using harsh reducing agents such as $LiAlH_4$. (Scheme 1.5.53.)



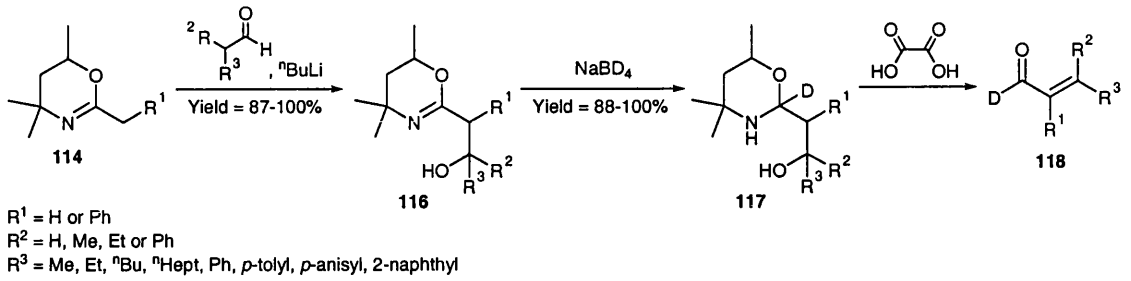

**Scheme 1.5.53.** Sodium borohydride reduction of nitriles and amides *via* the imino ether intermediate.

Reduction strategies have often been combined with *aza*-enolate alkylation reactions to afford powerful synthetic protocols. For example, Meyers *et al.* treated dihydrooxazines **114** (isomeric forms of lactim ethers) with BuLi and alkylated the resultant *aza*-enolate with a range of electrophiles.[80] Reduction of the resultant species with sodium borohydride gave access to α-substituted aldehydes, whilst reduction using sodium borodeuteride allowed access to the corresponding isotopically labelled analogues **115**. (Scheme 1.5.54.)



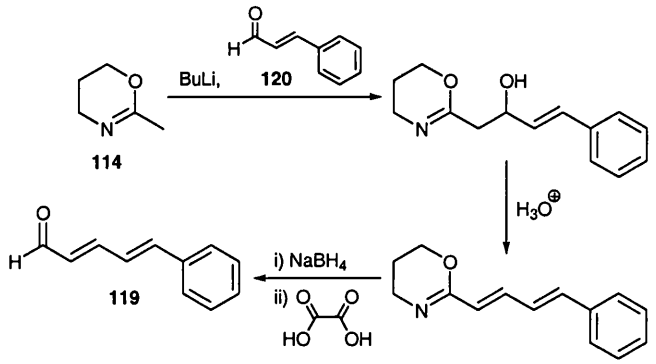

**Scheme 1.5.54.** *Aza*-enolate alkylation and reduction of an oxazine **114** to afford isotopically labelled α-alkyl aldehydes **115**.

Alkylation of *aza*-enolates of these oxazine systems with aldehydes affords alcohols **116**, which in turn could be reduced to their corresponding aldol products **117**, which on treatment with oxalic acid resulted in elimination/hydrolysis to afford α,β-unsaturated aldehydes **118**. (Scheme 1.5.55.)




**Scheme 1.5.55.** Reaction of the *aza*-enolate of a dihydrooxazine **114** with an aldehyde to afford the isotopically labelled α,β-unsaturated aldehyde **118**.

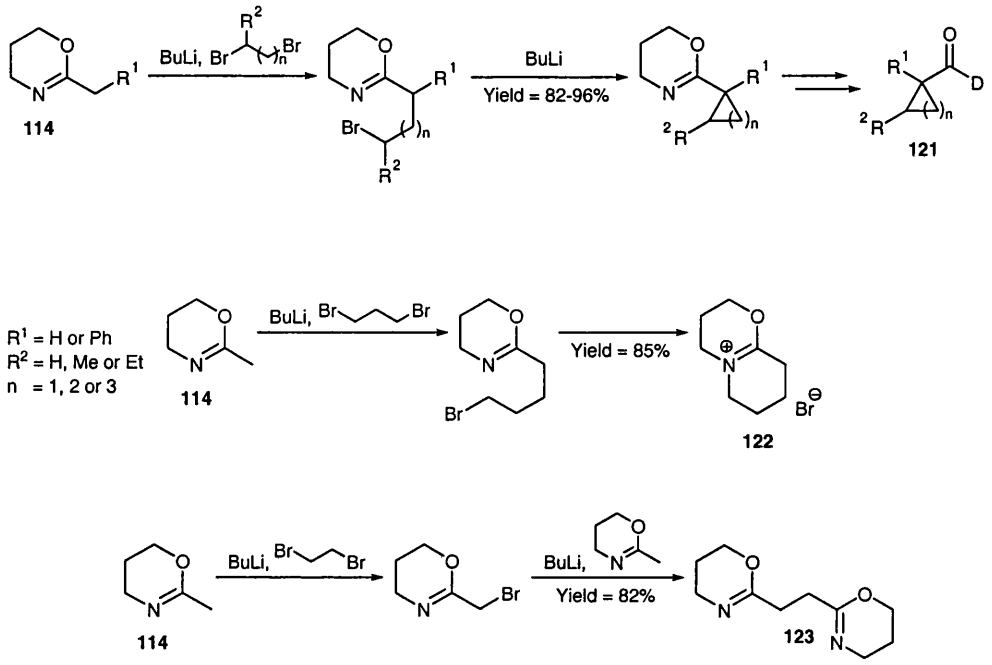
Meyers *et al.* also noted that α,β-unsaturated aldehydes could be used as electrophiles in this type of aldol reaction, thus affording a two carbon stereoselective chain extension of cinnamaldehyde in good overall yields to afford (*E*,*E*)-dien-aldehyde **119**.[81] (Scheme 1.5.56.)




**Scheme 1.5.56.** Stereoselective two carbon chain homologation of cinnamaldehyde **120**.

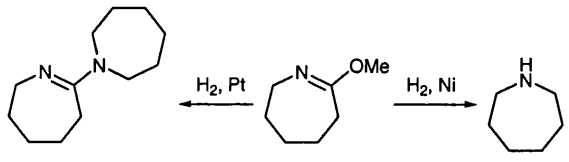
It was also reported that the oxizanes **114** could be dialkylated using *bis*-halo-electrophiles thus, enabling the efficient preparation of cyclic carboxaldehydes **121**.[82] In the case of 1,3-dibromopropane it was found that its ω-bromo intermediate **122** was

trapped by the nitrogen atom of the oxazinane. 1,2-dibromoethane acted as a bromine source and not as an alkylating agent, resulting in *aza*-enolate halogenation, which ultimately resulted in a dimeric product **123**. (Scheme 1.5.57.)




**Scheme 1.5.57.** Alkylation of dihydroxazines with electrophiles containing a second electrophilic centre.

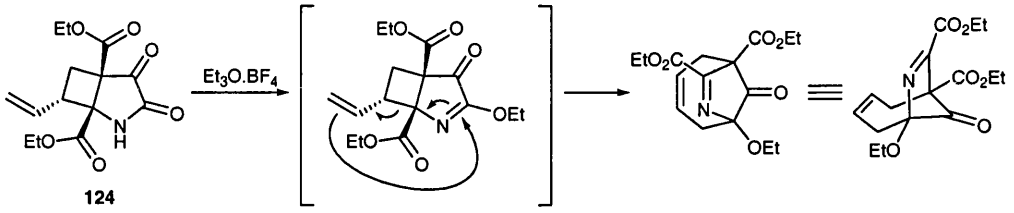
It has also been shown that lactim ethers are readily reduced using Raney nickel, ruthenium oxide and barium-copper chromite catalysts affording the corresponding cyclic imines in good yields.[16, 23] However, the use of a platinum catalyst has been shown to afford the corresponding amidine with piperidine and pyrrolidine derivatives being readily prepared *via* these approaches.[23] (Scheme 1.5.58.)




**Scheme 1.5.58.** Catalytic reduction of caprolactim ether **16**.

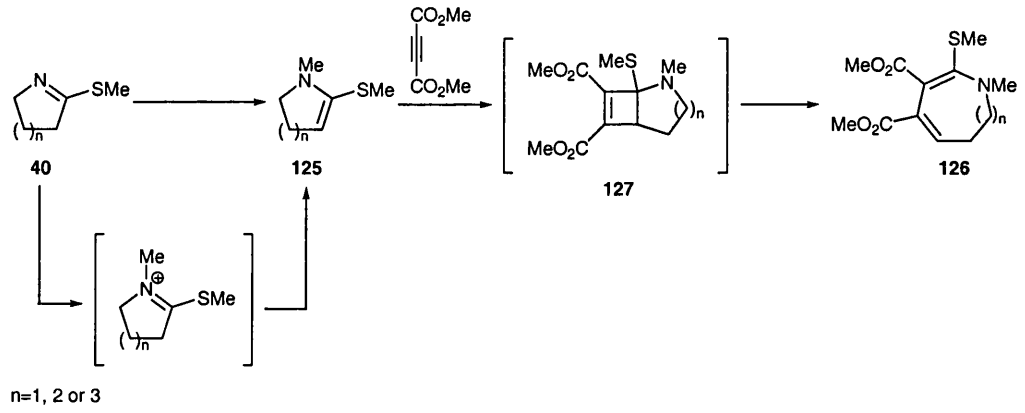
## 1.5.11. Pericyclic reactions of lactim ethers

There have been a number of reports on pericyclic reactions of lactim ethers. In 1992 Sano *et al.* observed an unexpected *aza*-Cope [3,3]-sigmatropic rearrangement of lactim ether **124** under conditions initially designed to favour photocycloaddition products.[83] (Scheme 1.5.59.)



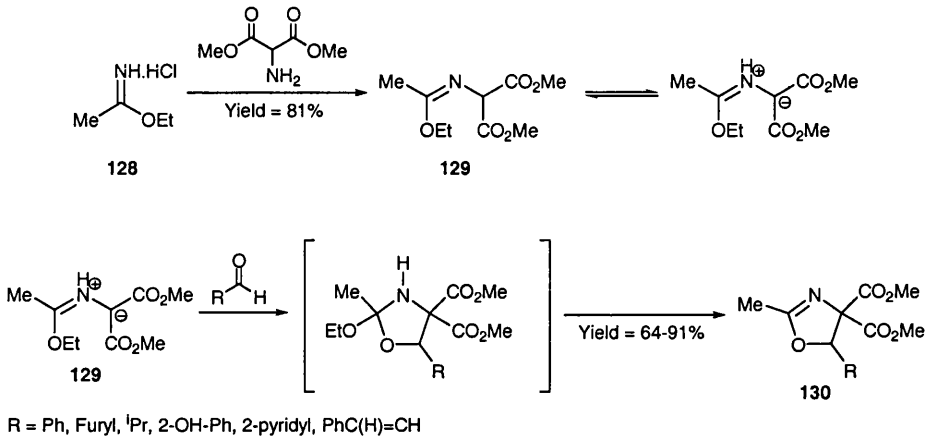

**Scheme 1.5.59.** Unexpected *aza*-Cope reaction of a diastereomeric imino ether **124**.

Yamazaki *et al.* have also shown that [2+2] cycloadditions could be performed on a related thiolactim ether substrate **40**.[84, 85] On *N*-methylation, the thiolactim ether underwent isomerisation to the enamine **125** that then underwent cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to ultimately afford substituted cyclic dieneamines **126**. Although the initial cyclobutyl product **127** was never isolated, the product of the electrocyclic ring opening reaction was observed as the major product. (Scheme 1.5.60.)



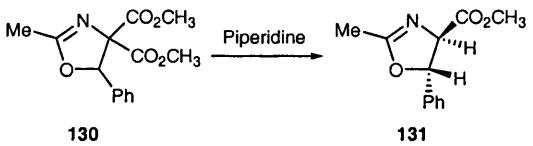

**Scheme 1.5.60.** [2+2] cycloaddition reaction of *N*-thiolactim ethers **40** and DMAD, followed by an electrocyclic ring opening.

Lerestif *et al.* demonstrated that reaction of dimethyl amino malonate with ethyl acetimidate hydrochloride **128** resulted in formation of a dipolarophile **129**, ideally suited for 1,3-dipolar cycloaddition reactions.[86] They reacted the dipolarophile **129** derived from dimethyl α-aminomalonate with a range of aldehydes thus generating the corresponding 2-oxazolines **130** in good yield. (Scheme 1.5.61.)




**Scheme 1.5.61.** Lerestif's 1,3-dipolar cycloaddition reaction of imino ether derived dipolaraphiles with aldehydes.

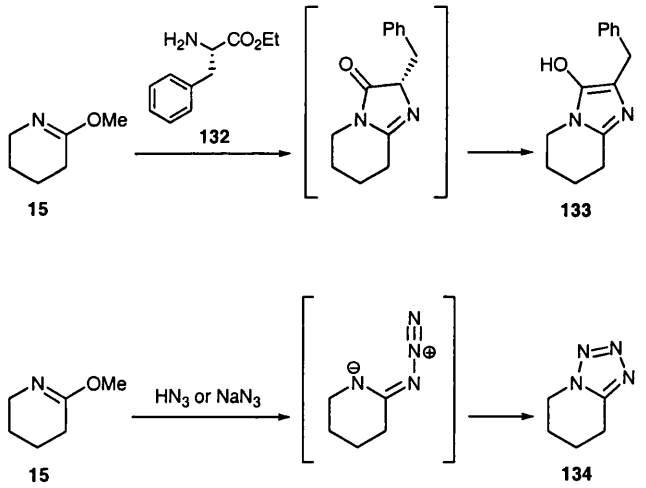
It was found that subsequent treatment of the resultant 2-oxazolines **130** with piperidine followed by heating to reflux in acetonitrile resulted in Krapcho decarboxylation to afford a *trans*-substituted oxazoline **131** in good yield. (Scheme 1.5.62.)




**Scheme 1.5.62.** Krapcho decarboxylation of Lerestif's oxazoline **130**.

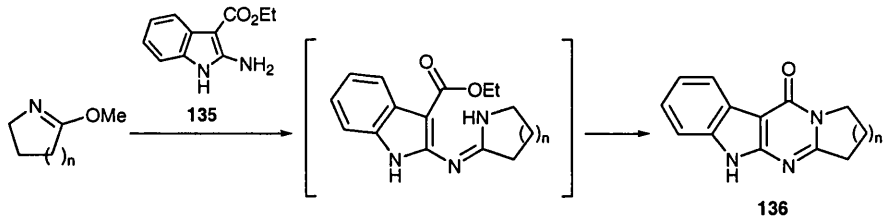
## 1.5.12. The use of lactim ethers for the synthesis of heterocyclic compounds

One of the most chemically and biologically important areas of modern organic chemistry is the development of the methodology for the synthesis of heterocycles. Imino and lactim ethers are ideal building blocks for the synthesis of a wide range of structurally complex heterocycles, owing to the electrophilicity of their alkyloxy units and the nucleophilicity of their imidic nitrogen atoms. One of the most commonly employed routes is to react a lactim ether with a substrate that contains complimentary electrophilic and nucleophilic centres, thus enabling intramolecular coupling and intramolecular ring cyclisation reactions to be carried out in a single step.[39 87, 88] This approach is demonstrated for reaction of valerolactim ether **15** with α-amino ester **132**, and azides which afforded excellent yields of the desired bicyclic heterocycles **133** and **134**. (Scheme 1.5.63.)



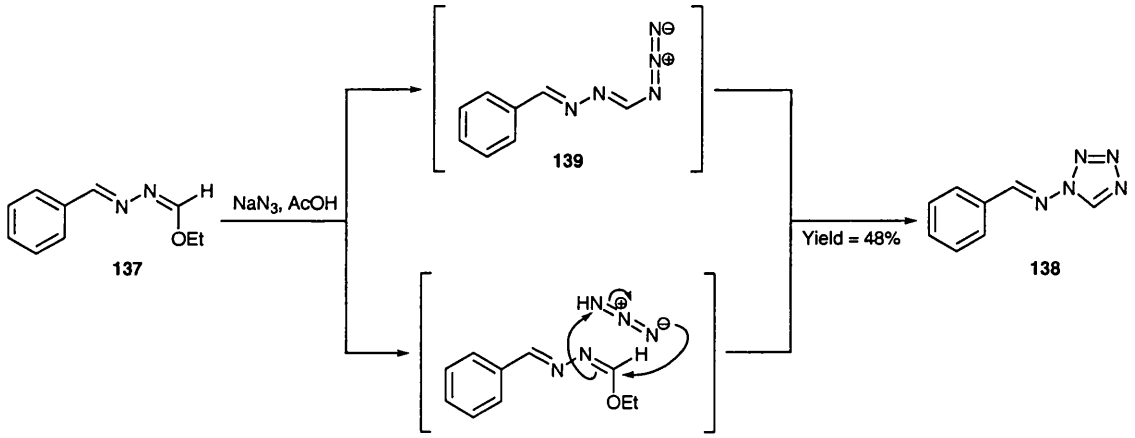

**Scheme 1.5.63.** One step heterocyclic formation reactions using valerolactim ether **15**.

In 1975 Wamhoff *et al.* showcased the fact that the electrophilic nature of the $sp^2$ carbon atom of lactim ethers could be combined with the nucleophilicity of the $sp^2$ nitrogen atom to afford families of heterocyclic compounds.[89] Treatment of β-amino esters **135** with a series of lactim ethers resulted in the rapid generation of complex multicyclic compounds **136** in good yield. (Scheme 1.5.64)



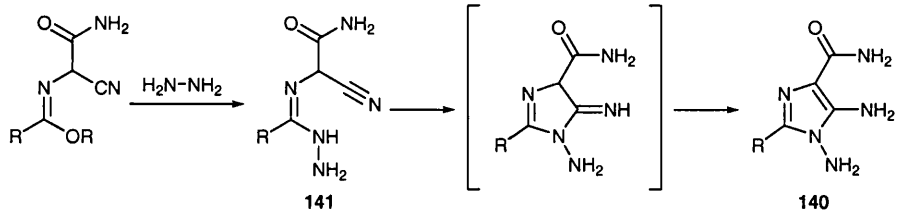
**Scheme 1.5.64.** Wamhoff's synthesis of a tetracyclic structure **136** using lactim ethers.

In 1966 Winkelman and Hagedorn treated ethyl *N*-benzylimine formimidate **137** with sodium azide and reported formation of phenyl-*N*-(1H-tetrazol-1-yl)methanimine **138**. [87, 88] It has been speculated that the process proceeds though an azido amidine structure **139** that cyclises intramolecularly, however it is possible that the reaction may proceed through a 1,3-dipolar cycloaddition reaction. (Scheme 1.5.66.)



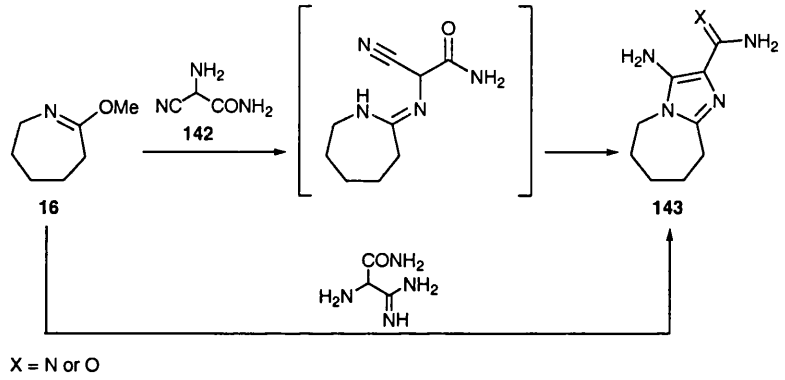
**Scheme 1.5.66.** Tetrazole formation from reaction of azides with imino ethers.

Attack of amines, and especially hydrazines, upon imino ethers can be utilised to generate heterocycles intramolecularly provided there is a second electrophilic site available. In 1961 Naylor *et al.* employed this approach in their synthesis of substituted imidazoles **140**.[90] Once the hydrazine had attacked the imino ether to form an intermediary hydrazine derived amidine **141**, the molecule was able to cyclise *via* intramolecular attack of its secondary amine on the cyano group. (Scheme 1.5.67.)



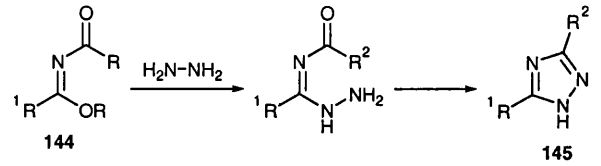
**Scheme 1.5.67.** Naylor's synthesis of substituted imidazoles.

In 1961 Glushkov showed that reaction of caprolactim ether **16** with α-amino-α-cyanoacetamides **142** gave 1,2-pentamethylene-4-carboxamido-5-aminoimidazoles **143**.[13] They reported that the lactim ether **16** initially reacted with the nucleophilic amine functionality, followed by intramolecular cyclisation of its amino functionality onto the cyano group to afford an endocyclic amino group. (Scheme 1.5.68.)



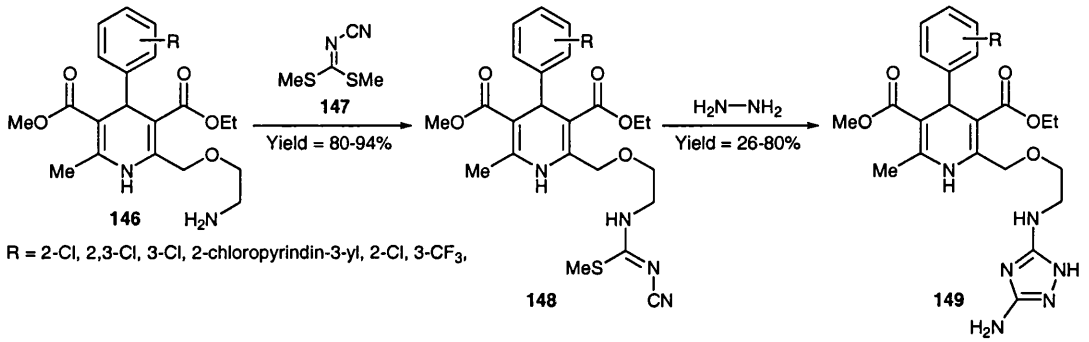
**Scheme 1.5.68.** Reaction of caprolactim ether **16** with α-amino α-cyanoacetamide **142**.

Baccar and Mathis also employed this approach for their parallel 1,2,4-triazole synthesis where reaction of hydrazine with *N*-acyl imino ethers **144** initially resulted in amidine formation, followed by intramolecular attack by the hydrazine terminal nitrogen atom to afford highly functionalised 1,2,4-triazoles **145**. [91] (Scheme 1.5.69.)



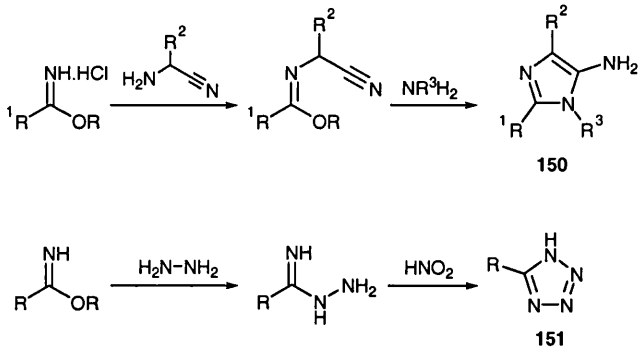
**Scheme 1.5.69.** Baccar and Mathis's 1,2,4-triazole synthesis.

Triazoles are present in many natural structures and medicinally active compounds since their high heteroatom content ensures solvation in aqueous media. For example, Arrowsmith *et al.* synthesised a sequence of triazole-dihydropyridines during their research into identifying selective coronary vasodilators.[92] They introduced a 1,2,4-triazole fragment *via* reaction of primary amine **146** with an *N*-cyano-dithioimino ether **147** to generate an *N*-cyanoamidino thioimino ether **148**. This thioamidino structure was then allowed to react with hydrazine which displaced the alkylthio fragment and then cyclised intramolecularly onto the cyano group affording the desired triazole **149**. (Scheme 1.5.70.)



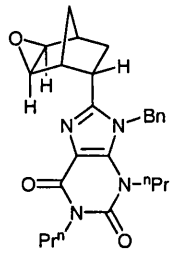

**Scheme 1.5.70.** Triazole **149** formation from the *N*-cyano-dithioimino ether **147**.

Other three component coupling strategies have also been developed for heterocyclic syntheses involving reaction of an imino ether with a nucleophile, followed by addition of a second reagent to induce ring closure, as shown for the formation of imidazoles **150** and tetrazoles **151**. (Scheme 1.5.71.)




**Scheme 1.5.71.** Imidazole **150** and tetrazole **151** formations using imino ethers.

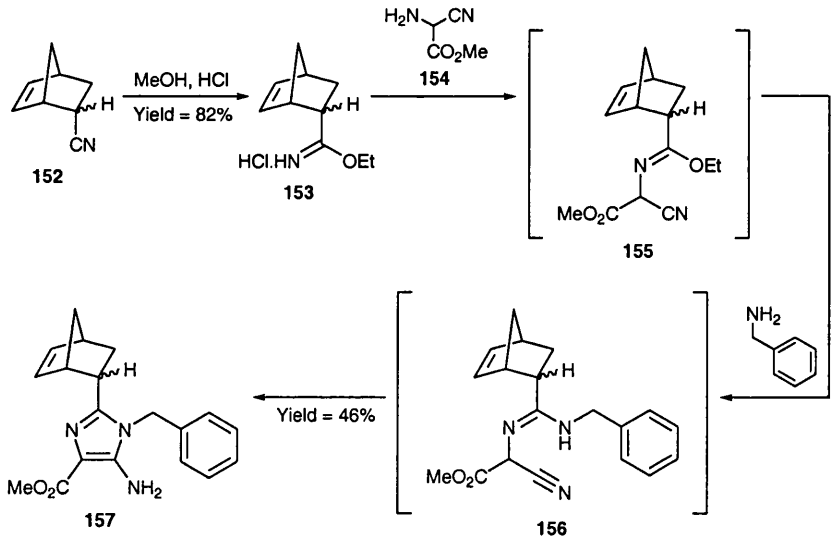
In 2002 Herr *et al.* published work detailing production of a late stage intermediate of chiral xanthine CVT-124,[93] which is a potent and selective adenosine A1 receptor antagonist that is currently undergoing phase II clinical trials.[94] (Figure 1.5.6.)




CVT-124

**Figure 1.5.6.** CVT-124.

They took a racemic mixture of 5-norbornene-2-carbonitrile **152** and carried out a Pinner reaction with methanol and HCl to furnish a racemic imino ether hydrochloride **153**. This mixture was then allowed to react with cyanoglycine methyl ester **154** to generate intermediary imino ether **155**, which was then treated with benzylamine to afford an amidine **156** that reacted intramolecularly to effect ring closure with formation of an exocyclic amine functionality **157**. (Scheme 1.5.72.)




152 153 155 156 157

**Scheme 1.5.72.** Synthesis of the norbornyl fragment of CVF-124.

The approach of combining an imino ether with a reactant that contains both an electrophilic and nucleophilic centre was employed by Wassermann *et al.* as

methodology for the total syntheses of the macrocyclic spermidine alkaloids (±)-dihydoperiphylline,[95] (±)-verbascenine,[96] and (±)-anhydrocannibisativine.[97, 98] (Figure 1.5.7.)

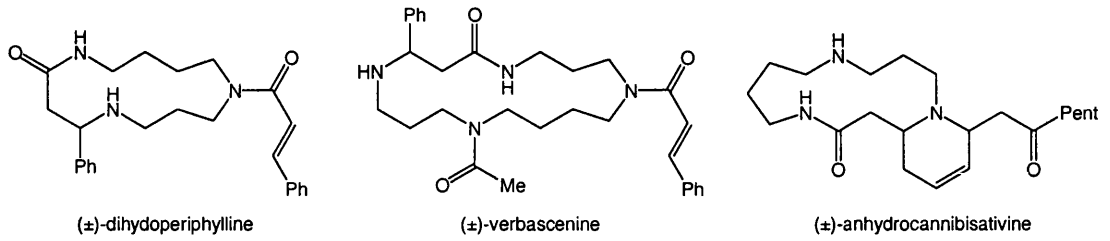
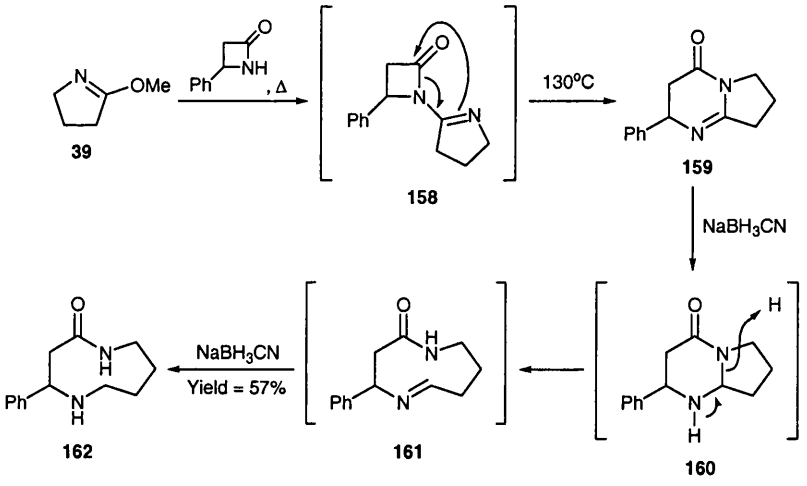


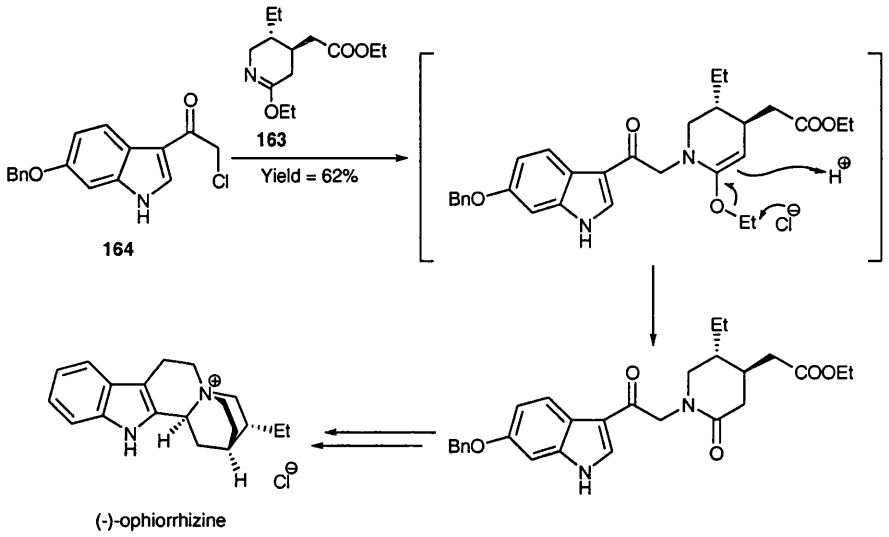

**Figure 1.5.7.** Structures of (±)-dihydroperiphylline, (±)-verbascenine and (±)-anhydrocannibisativine.

In this approach the author reacted β-lactams with butyrolactim ether **39** to generate a β-lactam amidine intermediate **158**,[21, 97, 98] that underwent intramolecular rearrangement to afford an amido dihydropyrimidine ring structure **159** on heating to 130 °C. They then reduced the resultant bicyclic compound **159** with sodium cyanoborohydride to afford 4-oxo-hexahydropyrimidine intermediate **160** which underwent tautomerisation to an amido imino structure **161** that was further reduced to afford the desired macrocyclic product core **162**. (Scheme 1.5.73.)



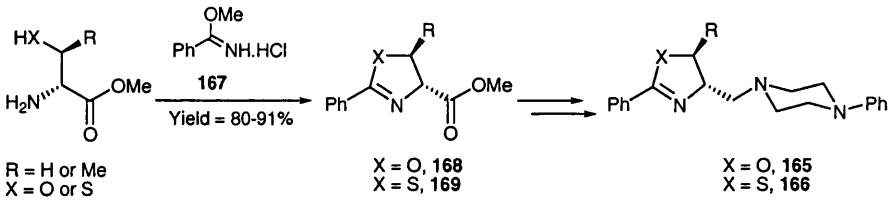

**Scheme 1.5.73.** Use of butyrolactim ether **39** for the synthesis of a series of macrocyclic spermine and spermidine alkaloids.

In 1995 Fujii *et al.* employed the nucleophilic nature of the nitrogen atom of a lactim ether as a key step in their convergent chiral synthesis of (-)-Ophiorrhizine,[99] an alkaloid isolated in 1992 from *Ophiorrhiza bracteata*[100] that has been reported for the treatment of eczema and other skin disorders.[101] They coupled a chiral lactim ether fragment **163** to an indole derivative **164** through its α-chloro ketone functionality, resulting in formation of a new amide group in place of the lactim ether moiety in 62% yield.[99] (Scheme 1.5.74.)



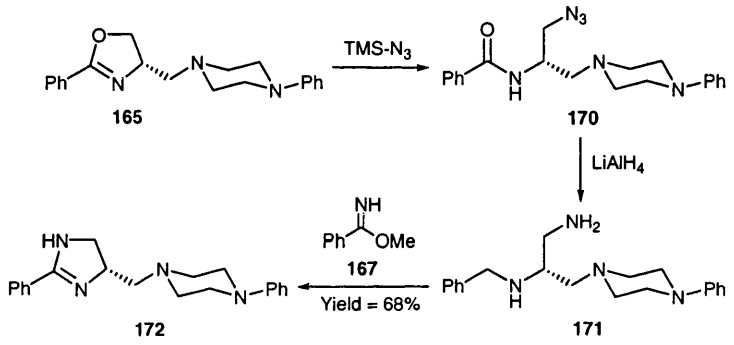

**Scheme 1.5.74.** A chiral lactim ether **164** being used in the synthesis of (-)-Ophiorrhizine.

Imino ethers have also been widely used as reagents to effect the ring closure of chiral 2-amino alcohols, or 2-amino thiols under acidic conditions.[1, 13, 102] This approach was employed by Gmeimer *et al.* for the synthesis of a series of conformationally restricted benzamide bioisosteres as highly selective dopamine D4 receptor inhibitors.[103] The strategy employed for the formation of the dihydroimidazoles **165** and dihydrothiazoles **166** was based on condensation of methyl benzimidate **167** with either (*R*)-serine methyl ester hydrochloride or (*2R*,3*S*)-threonine methyl ester hydrochloride to afford the corresponding dihydrooxazole **168** or dihydrothiazole species **169**, which were then further functionalised to afford dihydroimidazoles **165** and dihydrothiazoles **166.** (Scheme 1.5.75.)



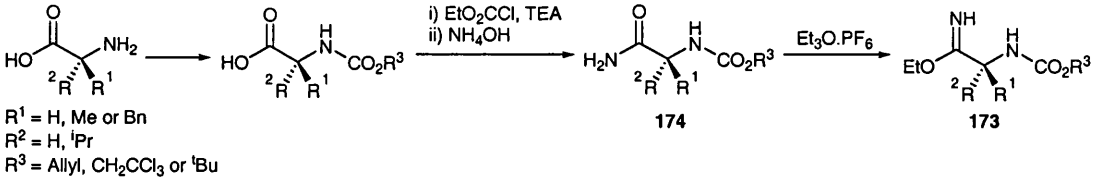

**Scheme 1.5.75.** Synthesis of dihydrooxazoles and dihydrothiazoles from methyl benzimidate **167**.

Nitrogen analogues were subsequently prepared *via* a ring opening amination step of the parent dihydrooxazole **165** using trimethylsilyl azide as a nucleophile to generate an azido amide compound **170**, which was reduced using $LiAlH_4$ to the corresponding diamine **171**. This diamino species **171** was then treated with methyl benzylimidate **167** under acidic conditions to furnish the desired imidazoline **172**. (Scheme 1.5.76.)




**Scheme 1.5.76.** Synthesis of the imidazole analogue **172**.

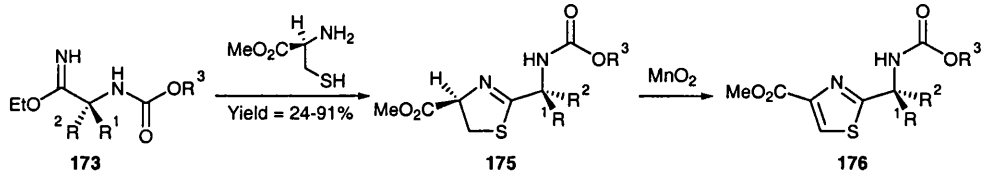
Sulfur based nucleophiles may also be used for the synthesis of chiral heterocyclic products. In 1990 Pattenden *et al.* prepared a range of *N*-protected imino esters **173** from naturally occurring L-amino acids.[104] They converted the intermediary amide **174** into its corresponding imino ether **173** *via* treatment with triethyloxonium hexafluorophosphate, as triethyloxonium tetrafluoroboronate had resulted in extensive cleavage of the amine protecting groups. (Scheme 1.5.77.)




$R^1$ = H, Me or Bn
$R^2$ = H, $^i$Pr
$R^3$ = Allyl, $CH_2CCl_3$ or $^t$Bu

**Scheme 1.5.77.** Formation of *N*-protected imino ethers **173** from the corresponding amino acid.

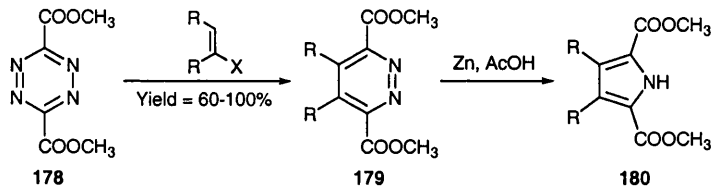
The group then condensed a series of these imino ethers **173** with the amine and thiol group of (*R*)-cysteine methyl ester to afford enantiomerically pure thiazolines **175**, which were easily oxidised to their corresponding thiazoles **176**. As expected, the stereochemical integrity at both stereogenic centres of the thiazoline intermediate **175** was retained, although the thiazoline **176** stereocentre was lost during the subsequent aromatisation reaction. (Scheme 1.5.78.)

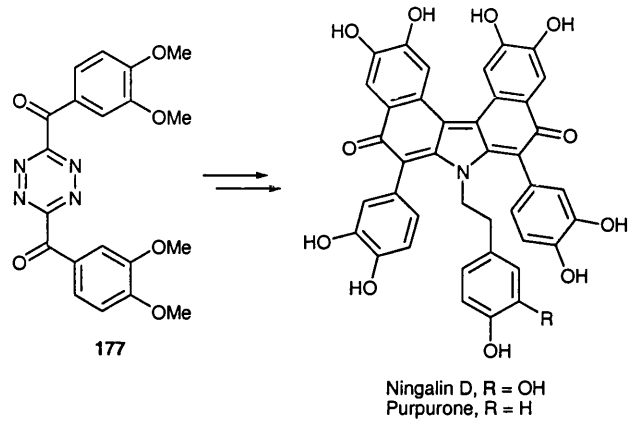



$R^1$ = H, Me or Bn
$R^2$ = H or $^i$Pr
$R^3$ = Allyl, $CH_2CCl_3$, Bn or $^t$Bu

**Scheme 1.5.78.** Synthesis of chiral thiazolines **175** and thiazoles **176**.

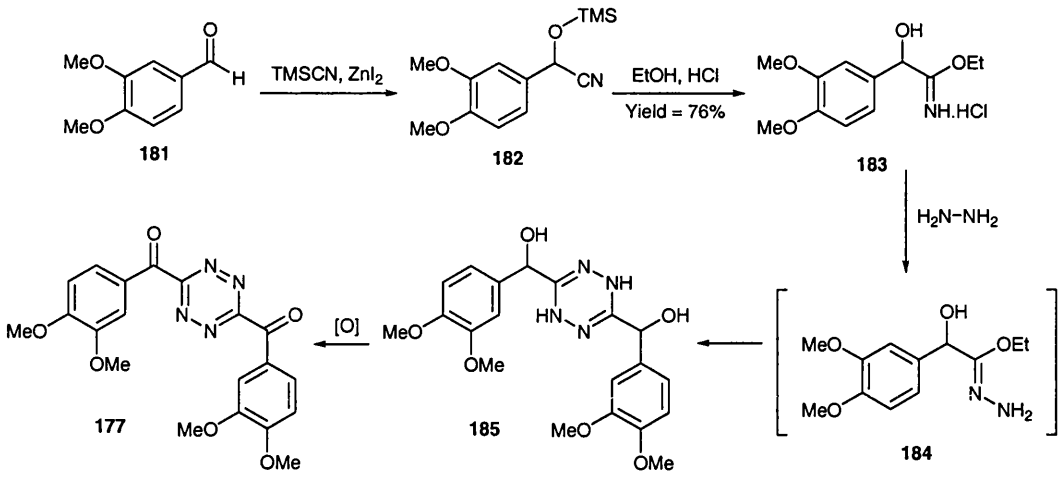
Tetrazines are also readily formed through the use of imino ether intermediates. A powerful example of this type of approach was demonstrated by Boger *et al.* for the preparation of a 3,6-*bis*-(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine intermediate **177** during his total synthesis of ningalin D and purpurone.[105] Previous work had employed dimethyl dicarboxylate **178** for Diels-Alder reactions with a wide range of dienophiles for the formation of a new aromatic ring through loss of nitrogen. This approach was a very effective strategy for synthesising 1,2-diazines **179** as both electron rich and electron deficient dienophiles could be used for synthesis. These types of pyridazines are easily transformed into pyrroles **180** *via* ring contraction reactions facilitated by the action of zinc and acetic acid. (Scheme 1.5.79)




**Scheme 1.5.79.** Generic overview of the synthetic scheme employed by the Boger group.

The 1,2,4,5-tetrazine **177** was synthesised in a 5 step process in 28% overall yield from 3,4-dimethoxy benzaldehyde **181**. In the initial step the group treated arylaldehyde with TMSCN to yield the TMS protected cyanohydrin **182**, which was subsequently reacted with ethanol in a Pinner synthesis to generate the desired imino ether hydrochloride salt **183**. Treatment of the imino ether **183** with hydrazine under acidic conditions resulted in transimidation to afford the *N*-amino imino ether **184**. Dimerisation of **184** to afford dihydrotetrazine **185**, followed by oxidative aromatisation with $FeCl_3$ and facile Dess-Martin oxidation of the benzylic alcohols gave a key synthetic intermediate **177** for the synthesis of ningalin D and purpurone. (Scheme 1.5.80.)




**Scheme 1.5.80.** Boger's tetrazine **177** synthesis.

## 1.6. Conclusion

This introduction section has demonstrated that imino ether and lactim ethers are versatile synthetic intermediates for the preparation of a wide range of heterocycles of use for drug discovery and for natural product synthesis.

The remainder of this thesis describes the development of synthetic methodology directed towards the use of the lactim ether moiety for synthesis. Specific interest has been focussed on three areas;

- Development of methodology for the alkylation of *aza*-enolates of the lactim ether functionality, followed by subsequent hydrolysis to afford α-alkyl ω-amino esters or α-alkyl lactams

- Development of alkyloxy substitution strategies of lactim ethers and its application for the development of asymmetric *aza*-enolate alkylation reactions using chiral auxiliary and chiral ligand strategies

- Development of synthetic strategies for the isotopic labelling of *bis*-lactim ethers for the asymmetric synthesis of isotopically enriched enantiopure α-amino acids

# Chapter 2

# Results and discussion

# Alkylation of the *aza*-enolates of lactim ethers

'...one in a million chances happen nine times out of ten...'

Terry Pratchett, Mort

# Chapter 2. Alkylation of the *aza*-enolate of lactim ethers for the synthesis of

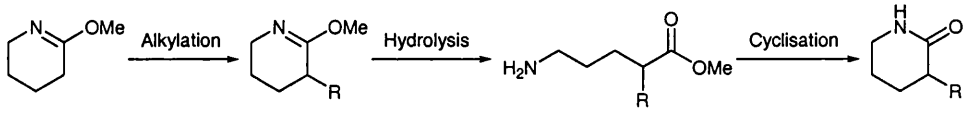
This job requires more memory than is available in this printer.
Try one or more of the following, and then print again:

- For the output format, choose Optimize For Portability.
- In the Device Settings page, make sure the Available PostScript Memory is accurate.
- Reduce the number of fonts in the document.
- Print the document in parts.

# Chapter 2. Alkylation of the *aza*-enolate of lactim ethers for the synthesis of α-alkyl ω-amino esters and α-alkyl lactams

## 2.1. α-Alkyl amino esters and lactams

This chapter describes the development of synthetic methodology for the synthesis of α-alkyl lactams and α-alkyl ω-amino esters through alkylation of *aza*-enolates of lactim ethers. It has been shown that lactim ethers can be deprotonated to afford their *aza*-enolates, which then undergo alkylation in the presence of an electrophile to generate their corresponding α-alkyl lactim ethers. It has also been demonstrated that hydrolysis of the α-alkyl lactim ethers affords the α-alkyl amino esters, which could be readily cyclised to afford their corresponding α-alkyl lactams. (Scheme 2.1.1.)




**Scheme 2.1.1.** Overview of the proposed strategy for the formation of α-alkyl ω-amino esters and α-alkyl lactams.

Consequently, a brief discussion of the current uses and methodologies used to prepare α-alkyl ω-amino esters and α-alkyl lactams now follows.

### 2.1.1. Current uses of α-alkyl lactams and ω-amino esters

α-alkyl lactams exhibit a wide and varied range of biological activities as demonstrated by their presence as fragments in natural products and medicinally active compounds. This biological activity predisposes them as pharmocophores for the preparation of a wide range of drug like molecules including AG7088 a human rhinovirus protease inhibitor,[106] and **186** which is an inhibitor for human cancer cell-lines that contains a derivatised caprolactam fragment.[107] (Figure 2.1.1.)

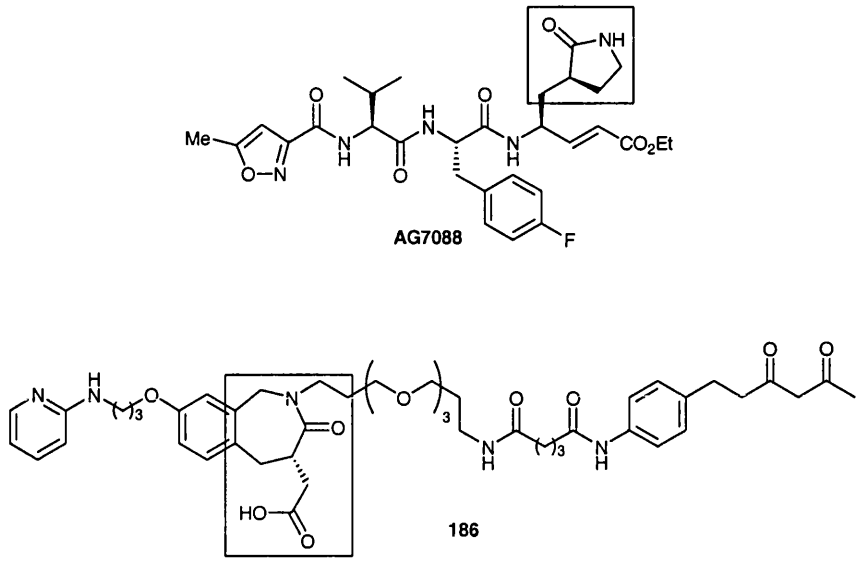



**Figure 2.1.1.** AG7088 a human rhinovirus 3C protease inhibitor containing an α-alkyl butyrolactam and **186** an RGD peptidomimetic that selectively binds to human cancer cells reducing tumour growth.

Given the recent success of α-alkyl α-amino acids, α-alkyl β-amino acids and butyro-amino acids in inducing secondary structure into short peptide fragments, α-alkyl ω-amino acids represent potentially attractive monomers for probing the conformation of derived peptidic isosteres.[108] They also represent a valuable class of synthetic compounds in their own right demonstrating a range of properties that make them desirable synthetic targets or intermediates. For example, **187** is a substrate analogue that acts as an inhibitor of chymotrypsin,[109] whilst dibutyro-peptide **188** was reported by Seebach to be a potent human somatostatin mimic.[110] (Figure 2.1.2.)

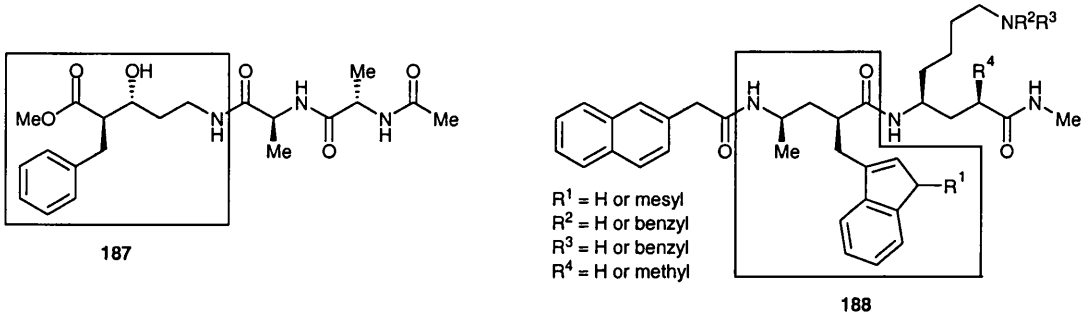
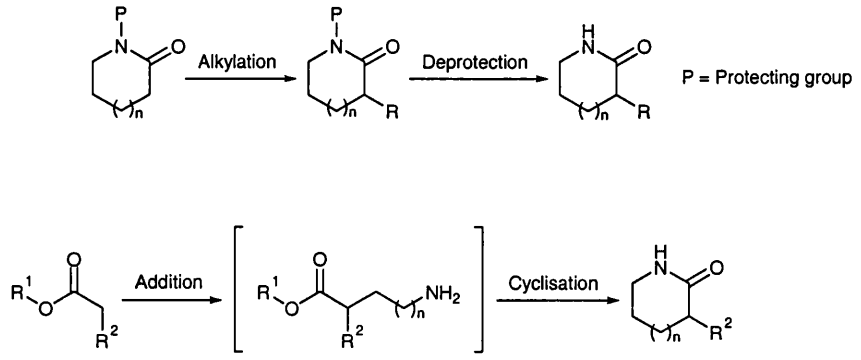



**Figure 2.1.2.** Chymotrypsin substrate analogue **187** that exhibits enzyme inhibition through acylation of key serine residues and human somatostatin mimic dibutyro-peptide **188**.

## 2.1.2. Current synthetic protocols for the production of α-alkyl lactams and ω-amino esters

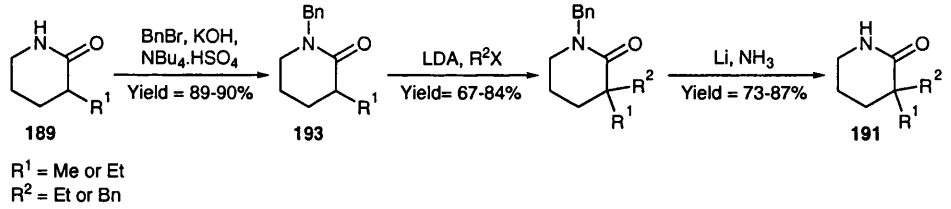
α-alkyl lactams have been prepared *via* many routes, However, the two main approaches currently employed involve direct alkylation of the enolate of a lactam, or alkylation of the enolate of a 'proamidic' compound such as an ester, which at a later stage undergoes ring closure to afford the α-alkyl lactam ring. (Scheme 2.1.2.)




**Scheme 2.1.2.** Preparation of α-alkyl lactams through direct alkylation of a lactams and through cyclisation of an α-alkyl amino ester.

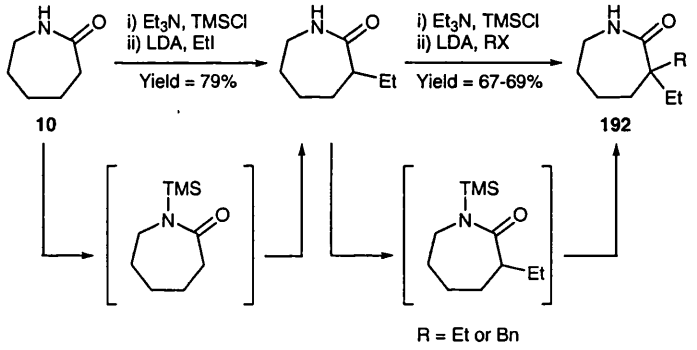
The first method is the most widely used, and many groups have reported the formation of α-alkyl and α,α-dialkyl lactams through its use. In this approach the nitrogen atom of the amidic bond often requires protection in order to avoid competing side reactions involving reaction of the nitrogen atom of the resultant metal amide with the desired electrophile. This method therefore requires a prior *N*-protection step and a subsequent deprotection step to remove the *N*-protecting group.

This methodology has been regularly employed owing to its wide applicability; for example Covey *et al.* alkylated α-alkyl valerolactams **189** and α-ethyl caprolactam **190** to prepare the corresponding α,α-dialkyl lactams **191** and **192** for use in anticonvulsant studies.[111] The group produced α,α-dialkyl valerolactams **191** through alkylation of the enolate of the *N*-benzyl *mono*-alkylated lactams **193**, before removing the *N*-benzyl protecting group using dissolving metal conditions. (Scheme 2.1.3.)




**Scheme 2.1.3.** Preparation of α,α-dialkyl valerolactam **191** from the parent lactam **189** through a benzyl *N*-protection pathway.

For the synthesis of α,α-dialkyl caprolactams **192** the authors switched to using a TMS group for *N*-protection of the lactam, thus demonstrating the stepwise production of two α,α-dialkyl caprolactams.[111] The group described that addition and removal of the TMS protecting group was more facile than for the benzylic analogue, involving *in situ* formations of *N*-TMS lactams, followed by aqueous desilylation during work up. (Scheme 2.1.4.)




**Scheme 2.1.4.** Preparation of α,α-dialkyl caprolactam **192** from caprolactam **10** through a sequential *in situ* *N*-TMS protection/enolate alkylation/deprotection approach.

A number of approaches involving prior formation of the skeleton for the desired lactam prior to cyclisation have been described. For example, in 2004 Chavan *et al.* employed a [3,3]-sigmatropic rearrangement of **194** to generate an α-alkyl lactam **195** as a building block for total synthesis of nothapodytine B, (±)-mappicine and camptothecin, as topoisomerase inhibitors for antitumour research.[112] (Figure 2.1.3.)

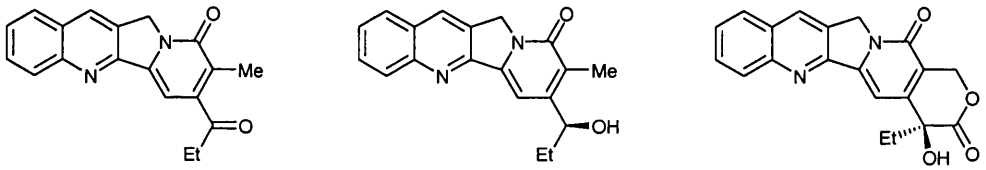
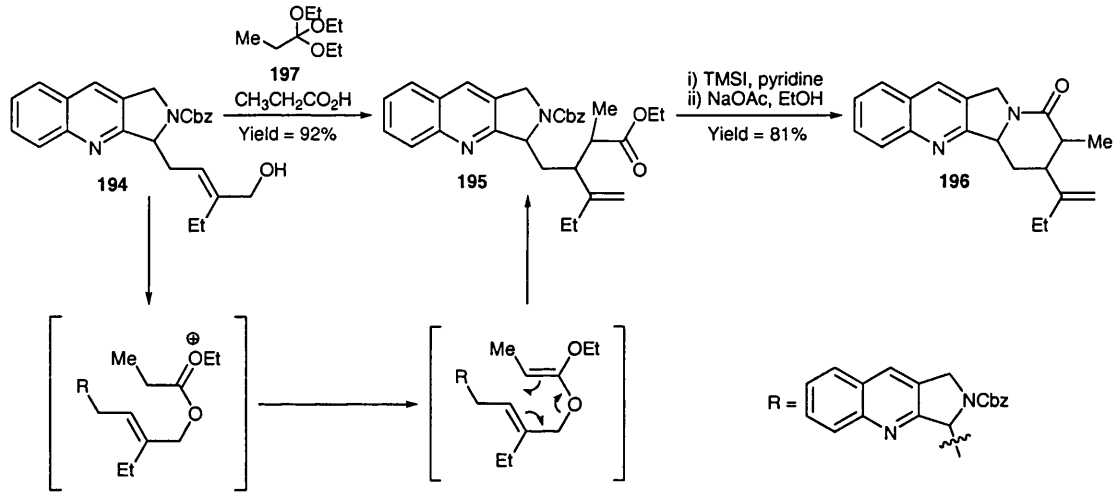



**Figure 2.1.3.** Structures of nothapodytine B, mappicine and camptothecin.

In this approach the pyridinone cores of **196** were produced *via* deprotection and cyclisation of the corresponding 'open chain' *N*-CBZ-protected α-methyl δ-amino ester **195**. The key intermediate **195** was formed by [3,3] sigmatropic rearrangement of **194**, formed *in situ* by esterification of its allylic alcohol with triethylorthoformate **197**. (Scheme 2.1.5.)

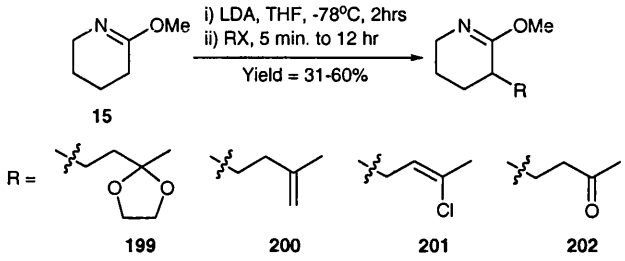



**Scheme 2.1.5.** Preparation, deprotection and cyclisation of an *N*-CBZ amino ester **194** affording a late stage intermediate **196** for the synthesis of nothapodytine B, mappicine and camptothecin.

It was proposed that alkylation of the *aza*-enolate of lactim ethers might provide an alternative route to this class of α-alkyl lactams, and as a consequence a brief review of the literature precedent for this class of transformation is now described.

## 2.1.3. Literature precedent for the alkylation of lactim ethers

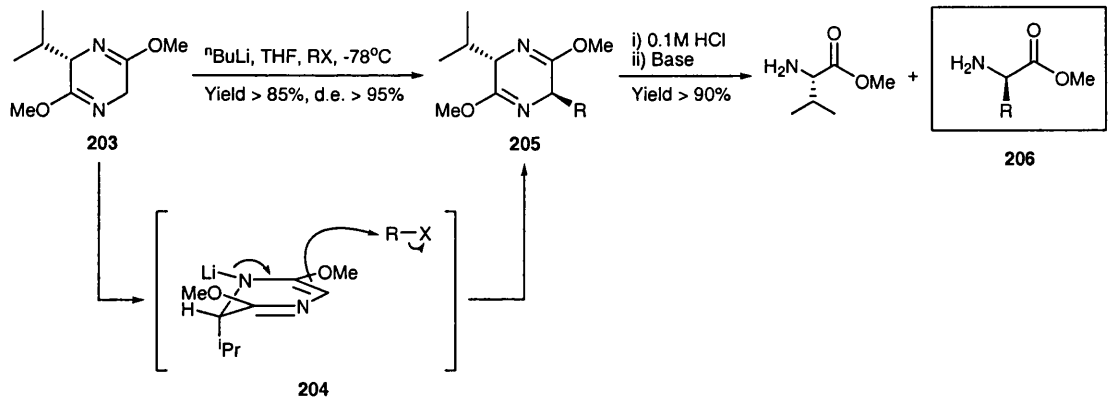
In 1974 Trost *et al.* showed that the *aza*-enolate of valerolactim ether **15** could be alkylated by electrophiles when he compared the alkylation properties of enolates of valerolactim ether **15** with the corresponding *N*-methyl lactam **198**.[113] They reported the use of this methodology for the synthesis of several α-substituted lactim ethers **199-202** in poor to moderate 31-60% yields. (Scheme 2.1.6.)




**Scheme 2.1.6.** Trost's alkylation of valerolactim ether **15** using LDA to generate the *aza*-enolate.

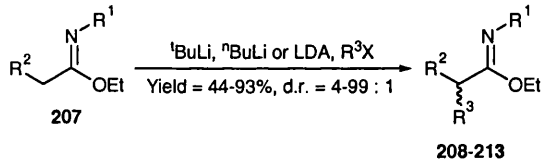
Trost also reported that the reaction did not proceed when $^{n}$BuLi was used as a base, and that only LDA and *N*-cyclohexyl-*N*-isopropyl amide were suitable for generating the desired *aza*-enolate species. This methodology has not been widely adopted by the synthetic community however, and we believed that its potential usefulness as methodology for the synthesis of α-alkyl ω-amino esters clearly warranted further investigation.

In contrast, a large number of reports have appeared in the literature in recent years describing the use of Schöllkopf's *bis*-lactim ether methodology for the asymmetric synthesis of α-amino acids. *Bis*-lactim ether **203** is deprotonated *via* the action of $^{n}$BuLi at low temperatures to afford a stabilised *aza*-enolate **204** that reacts with incipient electrophiles to afford a *trans*-alkylated-*bis*-lactim ether **205** in high yields and d.e.[114-119] Subsequent deprotection of the *trans*-alkylated *bis*-lactim ether **205** *via* mild acid catalysed hydrolysis affords the desired enantiopure α-amino ester **206**. (Scheme 2.1.7.)




**Scheme 2.1.7.** Schöllkopf's asymmetric alkylation of the *aza*-enolate of a *bis*-lactim ether **204**, with subsequent hydrolysis to afford an enantiopure α-amino ester **206**.

Further to the well documented methodology of Schöllkopf detailing the alkylation of *aza*-enolates of this type of cyclic lactim ethers, Bergbreiter and Newcomb published work in 1984 describing the alkylation of *aza*-enolates of acyclic imino ethers **207** for the asymmetric synthesis of chiral α-alkyl carboxylic acid derivatives.[120] They reported that treatment of a small range of imino ethers **207** with strong base resulted in formation of the corresponding *aza*-enolate, which on treatment with a range of electrophiles afforded a series of α-alkyl imino ethers **208-213** in moderate to good yield, and generally high d.e. (Scheme 2.1.8.)



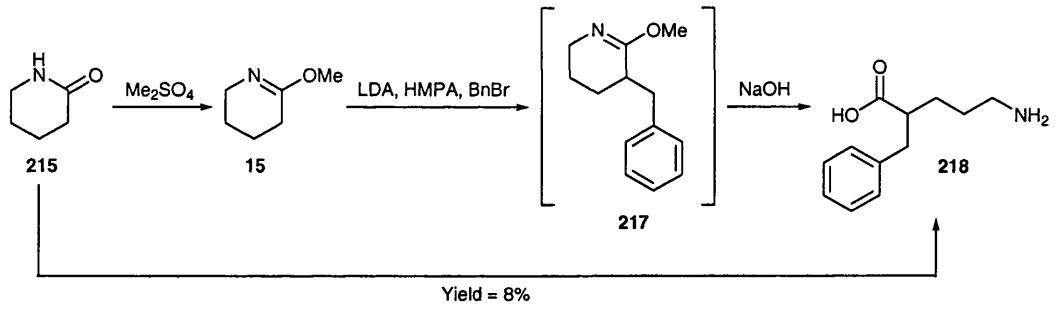

$R^1$ = (*R*) or (*S*)-CH($CH_2$Ph)$CH_2$OMe, (*S*)-CH($^i$Pr)$CH_2$OMe
$R^2$ = H or Me
$R^3$ = Me, Et, $^i$Pr, $^n$Pr, $^n$Bu or Bn

**Scheme 2.1.8.** Asymmetric alkylation of the *aza*-enolate of a chiral imino ether **207**.

| Entry | Ligand ($R^1$ =) | Electrophile | Yield/% | d.r. | Configuration[1] |
|---|---|---|---|---|---|
| 1 | (*S*)-CH(CH$_2$Ph)CH$_2$OMe | EtI | 70-80 | 19:1 | *R* |
| 2 | (*S*)-CH(CH$_2$Ph)CH$_2$OMe | BnBr | 80-85 | 32:1 | *R* |
| 3 | (*S*)-CH(CH$_2$Ph)CH$_2$OEt | MeI | 44 | 6:1 | *S* |
| 4 | (*S*)-CH(Ph)CH$_2$OEt | $^n$BuBr | 80 | 32:1 | *S* |
| 5 | (*S*)-CH(Ph)CH$_2$OEt | BnBr | 80 | 4:1 | *S* |

**Table 2.1.1.**

The only other report in the literature that could be found for the α-alkylation of lactim ethers was a low yielding synthesis by Lewis *et al.* of α-benzyl ω-amino acid **214** from valerolactam **215** in 1994.[121] They treated valerolactam **215** with dimethyl sulfate to afford the intermediary valerolactim ether **15**, which they then treated with LDA in HMPA to afford the *aza*-enolate **216** which they alkylated with benzyl bromide to afford α-benzyl valerolactim ether **217** that was then hydrolysed to afford the corresponding α-benzyl ω-amino acid **218** in 8% overall yield. This methodology was disregarded as a synthetic protocol owing to the very low yield and use of carcinogenic solvents. (Scheme 2.1.9.)

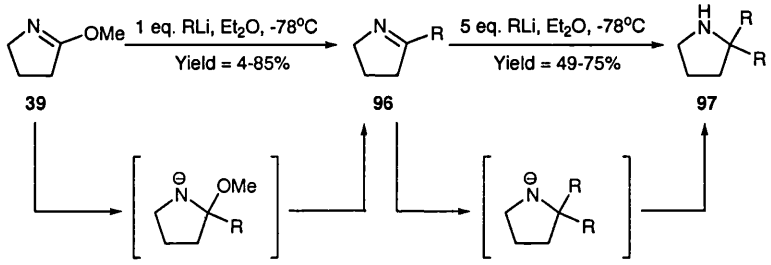



**Scheme 2.1.9.** Formation and alkylation of the *aza*-enolate of valerolactim ether **15** with subsequent hydrolysis to the corresponding α-benzyl ω-amino acid **218**.

[1] Configuration of the new stereocentre

## 2.1.4. Nucleophilic substitution reactions of lactim ethers

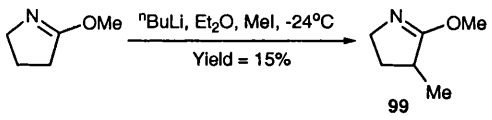
There is also contrasting literature precedent describing nucleophilic substitution reactions of lactim ethers with alkyl lithium or Grignard reagents.[13, 68, 70, 122] These substitution reactions proceed at low temperatures, with corresponding displacement of the alkyloxy group of the lactim ether by the nucleophilic alkyl fragment to afford cyclic imines **96**. In the presence of a large excess of alkyl lithium reagents the formation of tertiary dialkyl cyclic amine products **97** has been reported.[73] (Scheme 2.1.10.)




**Scheme 2.1.10.** Preparation of imines **96** and amines **97** from the parent lactim ether **39** *via* nucleophilic substitution.

## 2.1.5. Summary of literature precedent

These reports are paradoxical since the action of alkyl lithiums on lactim ethers can clearly result in the formation of different products arising from different reaction pathways, depending on whether the alkyl lithium acts as a nucleophile or as a base. For example, Schöllkopf's *aza*-enolate alkylation methodology is well documented to proceed in high yield to afford α-alkyl lactims, with no reports of the formation of any imine or amine products arising from a competing nucleophilic substitution pathway.[123-126] Alternatively, Glushkov, Lukeš, Červinka and Smith have all reported that nucleophilic substitution reactions of simple lactim ethers occur in preference to *aza*-enolate alkylation reactions.[13, 70, 72, 73] However, Smith *et* al. did note some evidence of an *aza*-enolate alkylation reaction for butyrolactim ether **39**, where they reported the formation of α-methyl butyrolactim ether **99** by a competing by product in 15% yield.[73] (Scheme 2.1.11.)



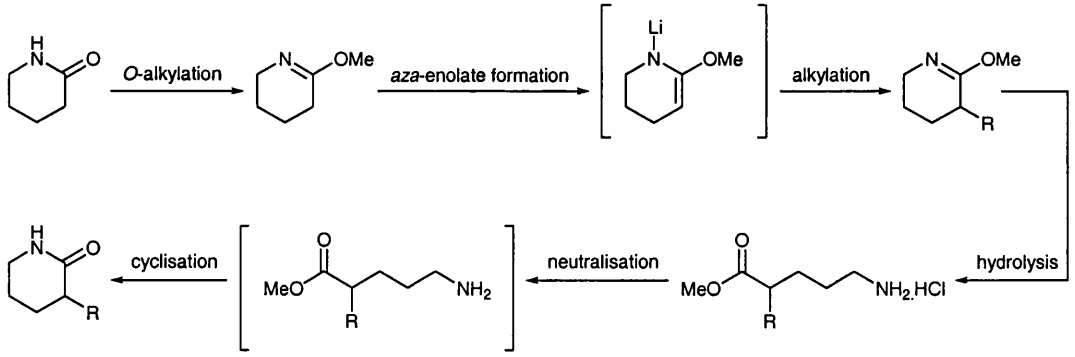

99

**Scheme 2.1.11.** Preparation of α-methyl butyrolactim ether **99** from a competing side reaction noted by Smith.[73]

It was felt that these unreconciled reports were worthy of further investigation, with a view to developing effective *aza*-enolate alkylation methodology applied to simple *mono*-lactim ether substrates, as success would afford methodology for the synthesis of divergent libraries of both α-alkyl ω-amino acids/esters, and α-alkyl lactams.

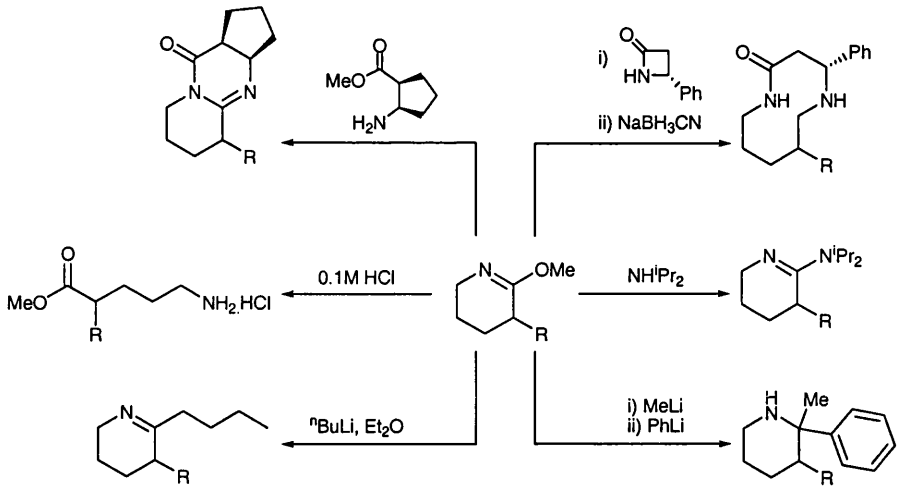
## 2.1.6. New approach to the synthesis of α-alkyl amino esters and lactams

An alternative strategy for the synthesis of α-alkyl lactams was proposed, in which a lactam was first converted to its more labile lactim ether, that would be deprotonated *via* the action of a base such as $^{t}$BuLi at low temperatures to afford an *aza*-enolate that would react with an electrophile to afford an α-alkyl lactim ether. The lability of the lactim ether bond could then be exploited using mild acidic hydrolysis to afford the corresponding ω-amino ester which would be isolated as its hydrochloride salt. While this type of ω-amino ester represents a valuable compound in a variety of disciplines, neutralisation would afford an intermediary amino ester which could potentially cyclise to afford an α-alkyl lactam. (Scheme 2.1.12.)




**Scheme 2.1.12.** Projected synthetic pathway to α-alkyl lactams using lactim ether substrates.

It was proposed that this synthetic protocol would provide versatile methodology that was superior to previous approaches for the synthesis of these class of compounds due to the improved physical properties of the lactim ether.[18, 47-50] Furthermore, it was proposed that several steps described in scheme 2.1.12. could potentially be combined into single pot transformations; for example hydrolysis of the α-alkyl lactim ether with mild acid followed by basification should directly afford a *mono*-alkyl lactam. Furthermore, as described in the introduction to this thesis, a wide range of methodology is available for converting lactim ethers into different functionalities. Thus, the resultant *mono*-alkyl lactim ethers would represent useful substrates for the synthesis of a wide range of heterocycles, amidines, amino acids, imines and amines. (Scheme 2.1.13.)



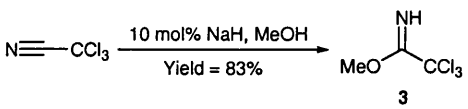

**Scheme 2.1.13.** Potential reaction products using α-alkyl lactim ethers as substrates.[27, 73, 96, 126-129]

## 2.2 Development of an effective synthetic protocol

Valerolactam **215** was initially chosen as a model substrate for *aza*-enolate alkylation studies due to its commercial availability, and was employed for the preparation of its corresponding lactim ether **15**.

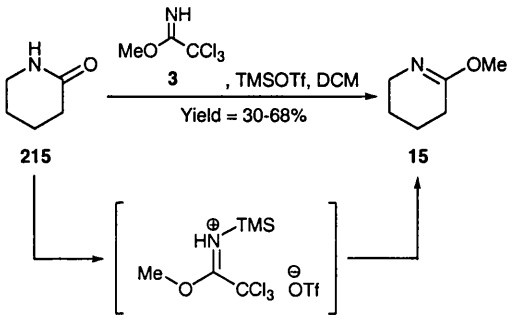
### 2.2.1 Preparation of valerolactim ether 15 using methyl trichloroacetimidate 3

Methyl trichloroacetimidate **3** represents a facile reagent for the preparation of lactim ethers and as such was prepared on a multigram scale according to literature precedent.[4] This Pinner synthesis proceeded cleanly *via* addition of methanol to trichloroacetonitrile under catalytic basic conditions, affording the desired compound **3** in 83% yield after purification by distillation. (Scheme 2.2.1.)




**Scheme 2.2.1.** Preparation of methyl trichloroacetimidate **3**.

Reactions aimed at *O*-alkylation of valerolactam **215** using methyl trichloroacetimidate **3** were carried out using a catalytic amount of TMSOTf, which afforded the desired lactim ether **15** in moderate yields ranging from 30-68%. (Scheme 2.2.2) However, this *O*-alkylation procedure proved capricious, and this fact coupled with the cost and handling difficulties associated with using moisture sensitive trimethylsilyl triflate, led to the development of an alternative approach for the synthesis of **15**.




**Scheme 2.2.2.** Preparation of **15** from valerolactam **215** using methyl trichloroacetimidate **3**.

## 2.2.2. Preparation of trimethyloxonium tetrafluoroboronate 221 (Meerwein's salt)

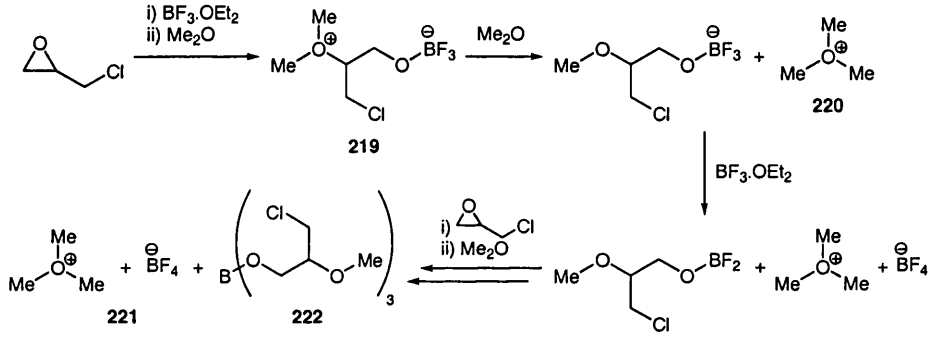
Trimethyloxonium tetrafluoroboronate **221** (Meerwein salt), $Me_3O.BF_4$, was then chosen as an *O*-alkylating reagent as it represented a reliable and facile reagent for the preparation of lactim ethers.[18, 130] Furthermore, it is a commercially available reagent, that can be stored for relatively long periods, is safe to use, and is highly chemoselective for *O*-alkylation over *N*-alkylation.[13]

Although Meerwein salt was commercially available there were some drawbacks associated with using this source of supply. The quality of reagent and delivery times from commercial suppliers was highly variable, whilst the cost of its use for large scale synthesis was also prohibitive.[2] Whilst initial work in this thesis employed commercially sourced Meerwein salt, it was quickly realised that significant quantities of this reagent would be required over the period of the research project. Consequently,

[2] Avocado, 2003-2004 catalogue, pg. 1369, cat. no. A15175, 50g, £103.

a reproducible synthesis of Meerwein salt was required that would enable its synthesis on a large multigram scale.

The preparation of $Me_3O.BF_4$ has been reported by several groups, However, the method described by Bull *et al.*[130] in 1998 involving modification of the original protocol of Curphey *et al.*[131] was selected. This reaction involves addition of $BF_3.OEt_2$ to a stirred solution of dimethyl ether and epichlorohydrin in $CH_2Cl_2$ at -20 °C. Coordination of the Lewis acid to the epoxide allows nucleophilic attack by dimethyl ether, resulting in ring opening to afford an intermediary oxonium compound **219**. This oxonium species **219** is then attacked by a second molecule of dimethyl ether to afford the desired trimethyloxonium core **220**, with sequential reactions affording the desired trimethyloxonium tetrafluoroboronate **221**, and a trihaloalkyl borate by-product **222**. (Scheme 2.2.3.) Fortunately, $Me_3O.BF_3$ is insoluble in $CH_2Cl_2$, and can be simply purified *via* filtration, thus affording 90% yields on a multigram scale.



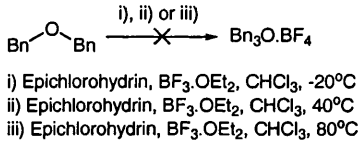

**Scheme 2.2.3** Mechanism for the formation of trimethyloxonium tetrafluoroboronate **221**.

## 2.2.3. Attempted preparation of tribenzyloxonium tetrafluoroboronate 223

Trialkyloxonium tetrafluoroboronates represent excellent reagents for *O*-alkylation of amides, being mild, selective, easy to use and safe to handle, however, only the trimethyl and triethyl versions are commercially available. Given the ease with which the trimethyloxonium salt had been prepared it was speculated that the potentially

useful tribenzyloxonium tetrafluoroboronate might also be prepared using this methodology.

However, repetition of the oxonium salt forming reaction using dibenzyl ether in place of dimethyl ether under a variety of conditions, failed to afford the desired tribenzyloxonium tetrafluoroboronate. This conclusion was confirmed *via* $^1$H NMR analysis of the crude reaction product since no salts were precipitated during the course of the reaction. Precedent for the formation of triethyloxonium tetrafluoroboronate indicated that this reaction might require gentle heating at reflux to proceed, therefore the reaction was repeated using dibenzyl ether at 40 °C, which once again failed to afford the desired product. In a final attempt the reaction temperature was increased to 80 °C, however, once again no formation of any tribenzyloxonium tetrafluoroboronate was observed. (Scheme 2.2.4.)

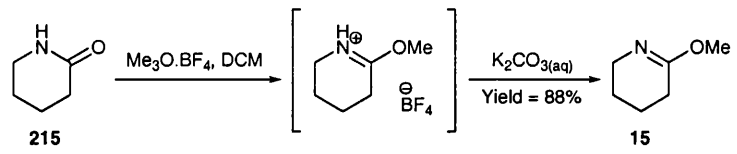



**Scheme 2.2.4** Unsuccessful attempted preparation of tribenzyloxonium tetrafluoroboronate.

## 2.2.4. Preparation of valerolactim ether 15

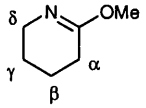
Synthesis of valerolactim ether **15** was then carried out *via* treatment of valerolactam **215** with Meerwein's salt in $CH_2Cl_2$ at room temperature, followed by neutralisation under basic conditions. Initial attempts to prepare valerolactim ether **15** were plagued by low yields of product associated with loss of the volatile product during removal of solvent during work up of the reaction. Furthermore, the lactim ether **15** is initially formed as its tetrafluoroboronate salt which is a highly acidic species that must be carefully neutralised at basic pH to prevent premature acidic hydrolysis of the lactim ether bond. Previous reports on the synthesis of Schöllkopf's *bis*-lactim ether chiral auxiliary stated that this could be achieved by addition of the highly acidic solution of related lactim ether salt to a rapidly stirred saturated aqueous solution of potassium

carbonate.[130] Adoption of this protocol enabled the lactim ether **15** to be reproducibly prepared in high yield, enabling its isolation in >80% yield on a multigram scale. (Scheme 2.2.5.)




215 15

**Scheme 2.2.5.** Preparation of **15** from valerolactam **215** using trimethyloxonium tetrafluoroboronate.



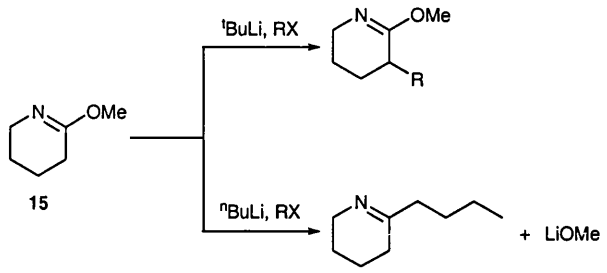

**15**

Analysis of the $^1$H NMR spectrum of valerolactim ether **15** revealed that it had been formed in high purity. Diagnostic resonances were observed for the methoxy group at δ 3.55 (s), the α methylene protons at δ 2.01 (dt, *J* 6.8 and 1.2 Hz) and the δ methylene protons at δ 3.41 (dt, *J* 5.7 and 1.2 Hz). The infrared spectrum showed a strong band at 1674 cm$^{-1}$ corresponding to the lactim ether functionality, as well as a molecular ion of 114.0914 ($M^+$, $CI^+$) in its mass spectrum.

## 2.2.5. Alkylation of valerolactim ether 15 to afford α-benzyl valerolactim ether 217

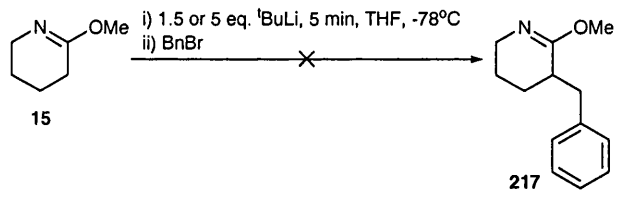
Following the precedent of Schöllkopf's *bis*-lactim ether methodology, it was decided to carry out initial *aza*-enolate alkylation attempts under similar conditions involving treatment with an alkyl lithium in THF at -78 °C for 5 minutes, followed by addition of an electrophile.[132] Since there was precedent for alkyloxy displacement reaction of lactim ethers by alkyl lithiums to afford their corresponding imines, it was decided to employ $^t$BuLi as a sterically demanding base which was less likely to react in a nucleophilic manner. This assumption followed from the observations of Smith *et al.*

who recorded far lower yields for the production of alkyl imines from lactim ethers when $^t$butyl lithium was used as a nucleophile.[73] (Scheme 2.2.6.)




**Scheme 2.2.6.** Potential pathways for the reaction of lactim ether **15** with alkyl lithiums.

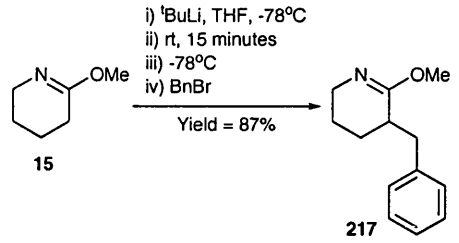
Preliminary *aza*-enolate alkylation reactions involved treatment of valerolactim ether **15** with 1.5 equivalents of $^t$BuLi in THF at -78 °C, for five minutes, followed by addition of 1.5 equivalents of benzyl bromide and allowing the reaction mixture to warm to room temperature overnight. The reaction mixture was then quenched by addition of dilute potassium carbonate solution in order to prevent premature hydrolysis of the lactim ether bond under acidic conditions. (Scheme 2.2.7.) This method failed to afford the desired benzylated lactim ether **217**, instead returning quantitative amounts of starting material **15**, with no reaction occurring even when large excesses of $^t$BuLi (up to five equivalents) were employed under identical conditions. (Scheme 2.2.7.)




**Scheme 2.2.7.** Unsuccessful attempted benzylation reaction of valerolactim ether **15**.

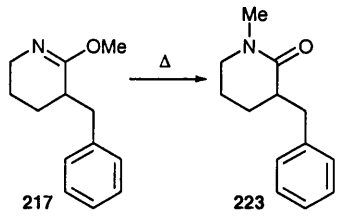
It was speculated that the lactim ether **15** had not been deprotonated by $^t$BuLi at -78 °C, so the reaction conditions were modified by treating the lactim ether with $^t$BuLi in THF at -78 °C, allowing the reaction mixture to warm to room temperature for 15 minutes, before recooling to -78 °C, prior to addition of benzyl bromide. This method was

successful affording the desired α-benzylated lactim ether **217** as the only observable product in the $^1$H NMR spectrum of the crude reaction product. (Scheme 2.2.8.)



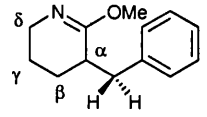

**Scheme 2.2.8.** Successful alkylation of the *aza*-enolate of valerolactim ether **15** to afford α-benzyl valerolactim ether **217**.

Purification of α-benzyl valerolactim ether **217** to homogeneity by column chromatography was attempted, however, significant decomposition on silica was observed as a result of the acidic and hygroscopic nature of silica with between 50-100% of crude product being lost during the chromatographic process. Attempts to resolve these decomposition problems by adding 1% triethylamine to the eluent were unsuccessful, whilst switching to alumina as a neutral stationary phase was only partially successful in affording better yields of the lactim ether product **217**. It was found however, that stringent drying of the silica in an oven at 130 °C did succeed in affording the benzylated lactim ether product **217** in moderate 51-81% yields. As a result of these difficulties an alternative distillation approach for purification of these lactim ether products was investigated, despite the fact that it has been reported that lactim ethers could undergo thermal rearrangement to their corresponding *N*-alkyl lactams **223**. (Scheme 2.2.9.)




**Scheme 2.2.9.** Chapman rearrangement of α-benzyl valerolactim ether **217**.

It was pleasing therefore to find that Kügelrohr distillation of the crude product resulted in very little loss of material affording α-benzyl valerolactim ether **217** in 87% overall yield, thus providing a simple purification route to this class of compound.



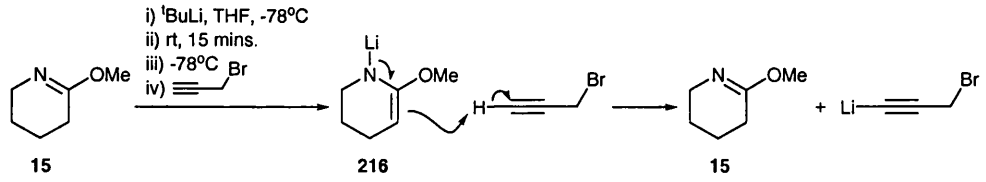

**217**

Analysis of the $^{1}H$ NMR spectrum of α-benzyl valerolactim ether **217** revealed the appearance of resonances at δ 2.55 and δ 3.12 as doublet of doublets, corresponding to the diastereomeric benzylic protons ($J_{gem}$ 13.2 Hz). The methoxy fragment was still present as a 3H singlet at δ 3.61, whilst a resonance corresponding to a single α-proton was observed as a multiplet at δ 2.38-2.49. Further to this, was the appearance of a broad multiplet between δ 7.07-7.25 corresponding to the five aryl protons of the benzyl fragment. The $^{13}C$ NMR spectrum revealed the presence of eleven resonances, whilst the IR spectrum revealed an absorption at 1674 $cm^{-1}$ for the lactim ether bond.

## 2.2.6. Preparation of a range of α-alkyl valerolactim ethers

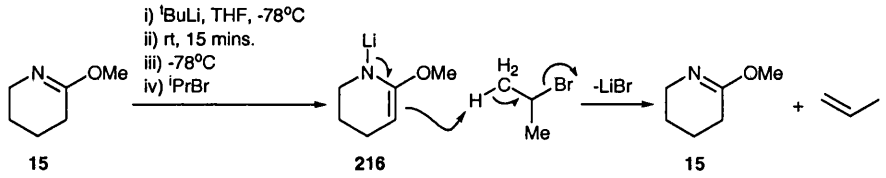
Given the excellent results obtained for alkylation of the *aza*-enolate of valerolactim ether **15** with benzyl bromide, work was undertaken to prepare a representative range of alkylated lactim ethers. In order to investigate the scope and limitations of this protocol a range of six electrophiles were employed as alkylating agents for these *aza*-enolate alkylation studies.

Methyl iodide was chosen as the second electrophile, as it represented a non-sterically demanding electrophile with moderate reactivity. The third electrophile of choice was allyl bromide as an electrophile with comparable reactivity to benzyl bromide, whose adducts would afford the opportunity for future functionalisation of the alkene bond *via* cross-metathesis, ozonolysis or hydroboration protocols. The fourth electrophile was propargyl bromide (as an 80% solution in toluene) which could potentially suffer from a competing side reaction involving deprotonation of the terminal alkynyl proton. (Scheme 2.2.10)



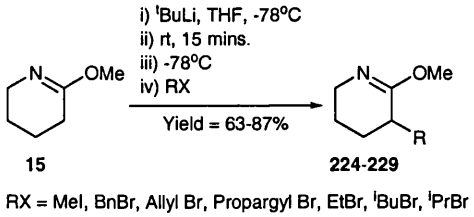

**Scheme 2.2.10.** Competing deprotonation pathway of propargyl bromide by the *aza*-enolate **216**.

The fifth choice was ethyl bromide as a test of the nucleophilicity of the *aza*-enolate towards a competing E2 elimination pathway. Finally, $^{i}$butyl bromide and $^{i}$propyl bromide were chosen as sterically demanding electrophiles that were readily available within the laboratory. (Scheme 2.2.11.)




**Scheme 2.2.11.** Competing E2 pathway of sterically demanding $^{i}$BuBr by *aza*-enolate **216**.

Consequently treatment of the *aza*-enolate of valerolactim ether **15** with these six electrophiles under optimised conditions afforded their corresponding *mono*-alkylated lactim ethers **224-229** in 63-87% yield after purification by Kügelrohr distillation. (Scheme 2.2.12.) Analysis of the $^{1}$H NMR spectra of the crude reactions products of *aza*-enolate reactions using electrophiles that could undergo a competing E2 elimination pathway (Table 2.2.2, entry 5-7) revealed the presence of some starting material **15**, although in <10% yield in each case. This indicates that the *aza*-enolate of **15** is non-basic and is an excellent nucleophile for both activated and sterically hindered electrophiles.




**Scheme 2.2.12.** Alkylation of the *aza*-enolate of valerolactim ether **15** with a range of electrophiles to afford α-alkyl valerolactim ethers **224-229**.

| Entry | Electrophile | Yield %[3] | $\delta_H$ OMe | $\delta_H$ α-H | IR/cm$^{-1}$ |
|---|---|---|---|---|---|
| 1 | BnBr | 87 | 3.61 | 2.38-2.49 | 1674 |
| 2 | MeI | 63 | 3.55 | 2.24 | 1674 |
| 3 | Allyl Br | 66 | 3.53 | 2.34-2.44 | 1674 |
| 4 | Propargyl Br | 78 | 3.54 | 2.52 | 1678 |
| 5 | EtBr | 68 | 3.53 | 2.04-2.15 | 1675 |
| 6 | $^{i}$BuBr | 64 | 3.52 | 2.13-2.24 | 1675 |
| 7 | $^{i}$PrBr | 83 | 3.53 | 2.13-2.24 | 1675 |

**Table 2.2.2**

All compounds were isolated and fully characterised demonstrating physical and spectroscopic data consistent with the formation of the monoalkyl lactim ether.

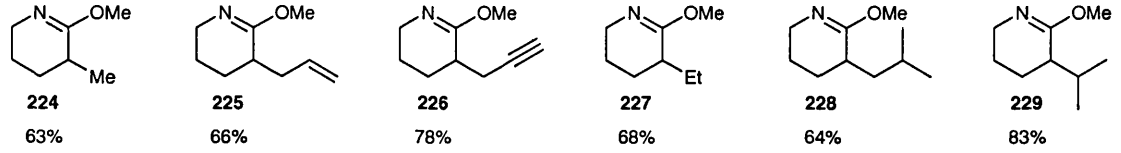



**Figure 2.2.13.** The range of α-alkyl valerolactim ethers **224-229** produced.

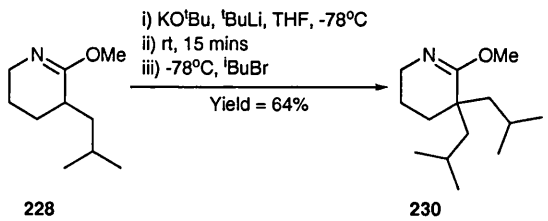
## 2.2.7. Preparation of α,α-dialkyl lactim ethers

Having established conditions that enabled *mono*-alkylation of valerolactim ether **15** attention then turned to the preparation of α,α-dialkyl valerolactim ethers. In order to

[3] After purification *via* Kügelrohr distillation

provide a challenging test of this methodology attempts to prepare α,α-di$^{i}$butyl valerolactim ether **230** were carried out, since it was considered that the steric demands of the $^{i}$butyl group, in conjunction with its potential to undergo an E2 elimination pathway, would make the α,α-di$^{i}$butyl lactim ether **230** a challenging target to test the effectiveness of this dialkylation protocol.

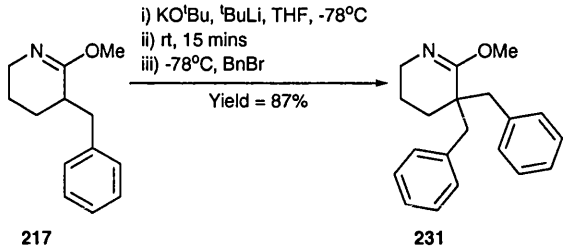
Initial attempts to alkylate the α-$^{i}$butyl lactim ether **228** under standard conditions developed previously involving addition of $^{t}$BuLi in THF at -78 °C followed by warming to room temperature and subsequent recooling to -78 °C after 15 minutes, afforded only recovered starting material **228** in quantitative yield. At this point it was speculated that $^{t}$BuLi might be too sterically demanding to deprotonate α-$^{i}$butyl lactim ether **228**, whilst exposing it to this aggressive base at room temperature for lengthy periods of time would lead to the formation of a large number of unwanted side products. As a result it was decided to investigate the use of other bases, and after screening a range of conditions it was found that using a mixture of either $^{n}$BuLi with KO$^{t}$Bu, or $^{t}$BuLi with KO$^{t}$Bu (Schlosser's base) was successful in affording *bis*-alkylated lactim ether **230**. Therefore, treatment of a solution of α-$^{i}$butyl valerolactim ether **228** in THF at -78 °C with 1.5 equivalents of KO$^{t}$Bu, followed by addition of 1.5 equivalents of $^{t}$BuLi, warming to room temperature for 15 minutes and consequent recooling to -78 °C, before addition of $^{i}$butyl bromide afforded the desired α,α-di$^{i}$butyl lactim ether **230** in 64% yield. The structure of α,α-di$^{i}$butyl valerolactim ether **230** was implicit from the simplicity of its $^{1}$H NMR and $^{13}$C NMR spectra as expected for this type of α,α-dialkyl lactim ether, which was confirmed from the observation of a molecular ion of 226.2165 in its mass spectrum. (Scheme 2.2.14.)




228 230

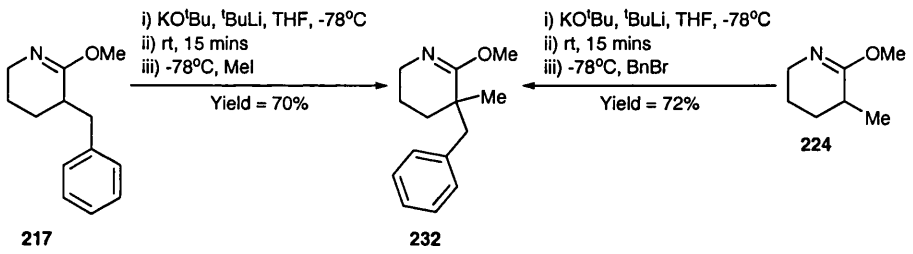
**Scheme 2.2.14.** Preparation of α,α-di$^{i}$butyl valerolactim ether **230** from α-$^{i}$butyl valerolactim ether **228**.

Formation of the *aza*-enolate of α-benzyl valerolactim ether **217** and subsequent alkylation with benzyl bromide under analogous conditions afforded α,α-dibenzyl valerolactim ether **231** in 87% yield, whose spectroscopic data was consistent with the formation of this product. (Scheme 2.2.15.)




**Scheme 2.2.15.** Benzylation of the *aza*-enolate of α-benzyl valerolactim ether **217** to afford α,α-dibenzyl valerolactim ether **231**.

The ability of this *aza*-enolate alkylation methodology to afford these type of sterically congested α,α-dialkylated valerolactim ethers is particularly noteworthy and testifies to the powerful nucleophilic character of this type of *aza*-enolate intermediate. In this regard, it was concluded that other types of disubstituted lactim ethers should be readily available using this methodology. As a final test of the efficacy of this protocol an unsymmetrical α,α-dialkyl lactim ether **232** containing a quaternary carbon stereocentre was then prepared *via* either methylation of the *aza*-enolate of α-benzyl valerolactim ether **217**, or benzylation of α-methyl valerolactim ether **224**, which proceeded in essentially identical 70-72% yields. (Scheme 2.2.16.)

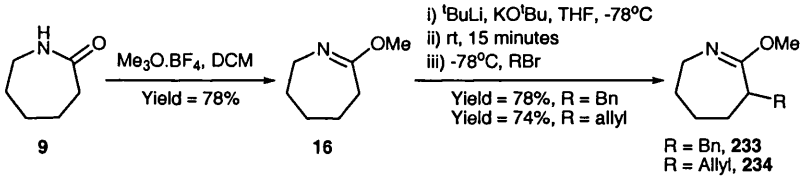



**Scheme 2.2.16.** Preparation of α-benzyl α-methyl valerolactim ether **232**.

# 2.3. Application of *aza*-enolate alkylation methodology to seven and eight membered lactim ethers

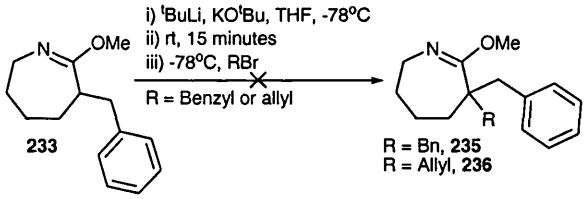
## 2.3.1. Synthesis of α-alkyl caprolactim ethers

The next extension of the use of this *aza*-enolate methodology was for the synthesis of α-alkyl caprolactim ether derived from caprolactam **10**. The caprolactim ether **16** was first prepared in 78% yield *via* treatment of caprolactam **10** with $Me_3O.BF_4$ in $CH_2Cl_2$ according to the previously established procedure. Unfortunately, attempts to alkylate the *aza*-enolate of caprolactim ether **16** using $^t$BuLi as a base under standard conditions were unsuccessful affording only recovered starting material. However, the use of the mixed $^t$BuLi/KO$^t$Bu basic system developed previously did afford the desired monobenzylated lactim ether **233** in 78% yield. A similar result was obtained using allyl bromide as an electrophile, which gave *mono*-allylated lactim ether **234** in 74% yield. (Scheme 2.3.1.) The spectroscopic and physical data of **233** and **234** were consistent with those previously obtained for their corresponding valerolactim ether analogues.




**Scheme 2.3.1.** Preparation and alkylation of the *aza*-enolate of caprolactim ether **16**.

Unfortunately, attempts to prepare α,α-dibenzyl caprolactim ether **235** *via* alkylation of the *aza*-enolate of α-benzyl-caprolactim ether **233** with benzyl bromide under a range of conditions were unsuccessful. Similar attempts to benzylate the *aza*-enolate of α-allyl caprolactim ether **234** were also unsuccessful, affording only returned starting material. (Scheme2.3.2.)




**Scheme 2.3.2.** Unsuccessful attempted alkylation of α-alkyl caprolactim ethers **233** and **234**.

| Entry | Reaction time/ minutes at rt | Equivalents of base | % yield of dialkyl product | % yield of recovered **233** |
|---|---|---|---|---|
| 1 | 15 | 1.5 | 0 | 78 |
| 2 | 60 | 1.5 | 0 | 65 |
| 3 | 15 | 3.0 | 0 | 81 |
| 4 | 60 | 3.0 | 0 | 71 |

**Table 2.3.1**

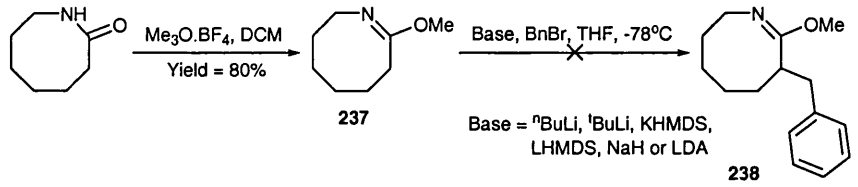
Attention then turned to the alkylation of the *aza*-enolates of eight membered lactim ethers.

## 2.3.2. Unsuccessful attempts to prepare α-alkyl oenantholactim ethers

Preparation of the eight membered lactim ether **237** using $Me_3O.BF_4$ proceeded in 80% yield, giving similar spectroscopic detail to that observed for the six and seven membered lactim ether analogues **15** and **16**.

Alkylation attempts on the *aza*-enolate of **237** under a wide range of conditions failed, including the use of the previously successful mixed base system ($^t$BuLi and KO$^t$Bu, 15 minutes at room temperature). This was a surprising result since the *aza*-enolate of the seven membered lactim ether **16** had alkylated readily under these conditions in high yield and purity, however no alkylation product was ever observed for this eight membered lactim ether substrate **237**. The *aza*-enolate alkylation reaction was attempted under a variety of conditions, including lengthy deprotonation times of two hours at room temperature, and a variety of base systems including $^n$BuLi, $^t$BuLi,

KHMDS, LHMDS, NaH and LDA. However, analysis of the $^1$H NMR spectra of the crude reaction products arising from any of these methods revealed no evidence of any of the desired α-benzyl oenantholactim ether product **238**. (Scheme 2.3.3.)



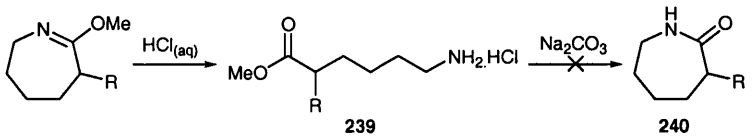

**Scheme 2.3.3.** Preparation and failed alkylation of oenantholactim ether **237**.

| Entry | Base system | Reaction time/ minutes at rt | Equivalents of base | % yield of α-benzyl lactim ether **238** | % yield of recovered **237** |
|---|---|---|---|---|---|
| 1 | $^n$BuLi/KO$^t$Bu | 60 | 2.0 | 0 | 65 |
| 2 | $^{tBuLi}$/KO$^t$Bu | 60 | 2.0 | 0 | 71 |
| 3 | $^n$BuLi | 60 | 2.0 | 0 | 70 |
| 4 | $^t$BuLi | 60 | 2.0 | 0 | 72 |
| 5 | KHMDS | 60 | 2.0 | 0 | 80 |
| 6 | LHMDS | 60 | 2.0 | 0 | 82 |
| 7 | NaH | 60 | 2.0 | 0 | 85 |
| 8 | LDA | 60 | 2.0 | 0 | 45 |

**Table 2.3.2.**

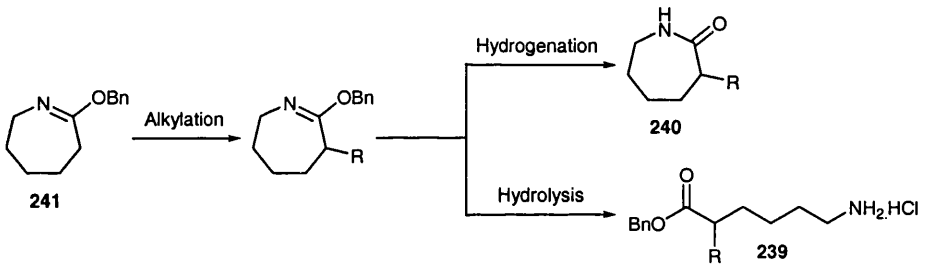
## 2.3.3. Preparation of benzyl capro and oenantholactim ethers using benzyl trichloroacetimidate 4

Whilst the use of methyl caprolactim ether **16** in *aza*-enolate alkylation reactions would provide a valuable route to the seven membered open chain amino esters **239**, this methodology was unlikely to be useful for the preparation of α-alkyl lactams **240** due to the difficulties encountered for the cyclisation of seven membered rings due to unfavourable torsional interactions in the transition state that generally favour oligomerisation of this class of monomer. (Scheme 2.3.4.)




**Scheme 2.3.4.** Failed cyclisation of a long chain amino ester **239**.

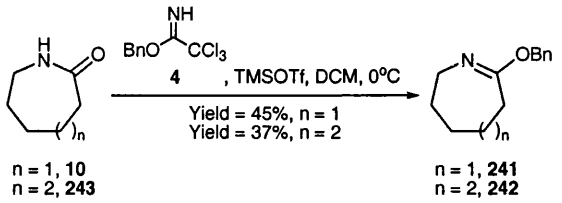
Therefore, an alternative strategy was sought for the synthesis of seven membered α-alkyl caprolactams involving a benzyl lactim ether substrate. This new benzyl lactim ether **241** would afford the possibility of directly affording a lactam ring, since hydrogenation would lead directly to the desired α-alkyl caprolactam **240**, whilst still allowing the alternative hydrolysis to its corresponding α-alkyl benzyl ester **239**. (Scheme 2.3.5.) Access was therefore required to multigram quantities of benzyl caprolactim ether **241**.




**Scheme 2.3.5.** Alternative synthetic pathway for the formation of large ring size lactams **240**.

Initial attempts to prepare capro **241** and oenantho **242** benzyl lactim ethers through the use of benzyl trichloroacetimidate methodology were plagued by poor yields, unreliability and problematic purification. Optimisation of the previously reported synthetic conditions,[6] involving treatment of the appropriate lactam with benzyl trichloroacetimidate **4** and a catalytic amount of TMSOTf in $CH_2Cl_2$ at 0 °C resulted in production of benzyl capro and oenantholactim ethers **241** and **242** in 45% and 37% yields respectively after column chromatography. It was found that the use of 0.5 equivalents of TMSOTf as a Lewis acid were required to achieve these relatively modest yields, which contrasts with previous reports that low catalytic levels of 10

mol% TMSOTF had afforded the best results for *O*-alkylation of lactams.[6] It was shown that losses in yield occurred primarily during purification of the crude reaction mixtures, with both chromatography and distillation resulting in significant losses in product, presumably *via* acid catalysed decomposition of benzyl lactim ether products **241** and **242**. (Scheme 2.3.6.)



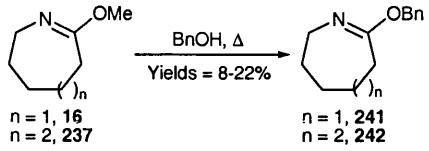

**Scheme 2.3.6.** Preparation of benzyl capro **241** and oenantholactim ethers **242** using benzyl trichloroacetimidate methodology.

## 2.3.4. Preparation of benzyl capro and oenantholactim ethers 241 and 242 using a transesterification approach with benzyl alcohol

Since the use of benzyl trichloroacetimidate **4** had proven unsatisfactory in providing good yields of benzyl lactim ethers **241** and **242**, attention turned to the synthesis of benzyl lactim ethers **241** and **242** through transesterification of the methoxy unit of the corresponding methyl lactim ethers **16** and **237** using benzyl alcohol. Reports in the literature suggested that facile removal of methanol from the reaction mixture *via* distillation would afford the desired benzyl lactim ethers **241** and **242** in good yield.[41, 43, 44] However, this method failed to produce the benzyl lactim ethers **241** and **242** in a reliable or reproducible yield which was ultimately ascribed to the lactim ether product being lost through distillation on account of the low yields of crude material reaction product recovered.

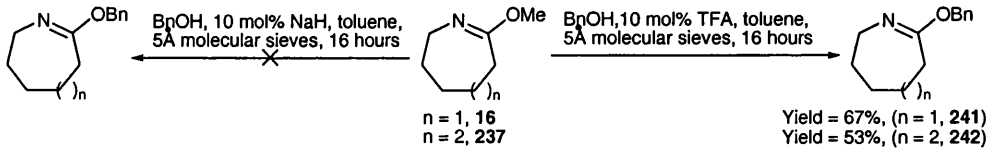
It was speculated that displacing the equilibrium of the transesterification reaction through addition of a large excess of benzyl alcohol (30 equivalents) should afford benzyl capro and oenantholactim ether **241** and **242** in increased yield under mild conditions. Whilst $^1$H NMR spectroscopic analysis of the crude reaction product showed that this method was successful in providing **241** and **242** in good conversion,

major problems were encountered during purification due to the large excess of benzyl alcohol used for the reaction, and whilst a pure sample of **241** and **242** could be obtained in poor yield through rigorous column chromatography this tedious approach was abandoned as impractical. (Scheme 2.3.7.)




**Scheme 2.3.7.** Transesterification of capro and oenantholactim ethers **16** and **237** with benzyl alcohol to afford **241** and **242**.

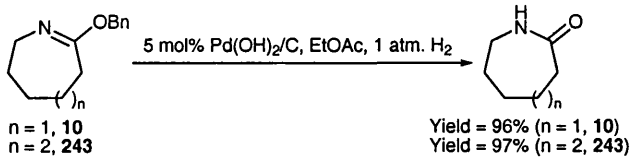
Previous reports had suggested that use of an alkoxide would result in a more efficient transesterification reaction.[1] It was found that when sodium benzoxide was employed as a nucleophile the rate of the transesterification reaction was retarded and the yield of benzyl lactim ethers **241** and **243** were found to be inferior to those achieved under neutral conditions. However, the use of acidic conditions to catalyse the transesterification reaction resulted in a higher yield of the desired benzyl lactim ether in good yield. Therefore, treatment of methyl lactim ethers **16** and **243** with benzyl alcohol in toluene in the presence of 1.3 equivalents of TFA and 5Å molecular sieves resulted in formation of benzyl lactim ethers **241** and **242** in 67% and 53% yields respectively. (Scheme 2.3.8.)




**Scheme 2.3.8.** Transesterification of caprolactim ethers **16** under basic and acidic conditions.

## 2.3.5. Hydrogenation of benzyl lactim ethers

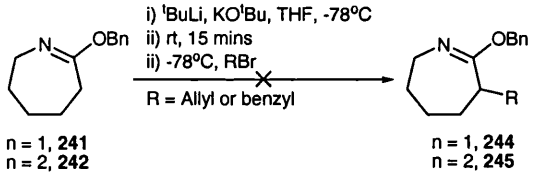
With benzyl lactim ethers **241** and **242** in hand, it was next demonstrated that they could be directly deprotected to their parent lactams *via* hydrogenation. As expected, treatment of benzyl lactim ethers **241** or **242** with catalytic levels (5 mol%) of palladium dihydroxide under one atmosphere of hydrogen in ethyl acetate resulted in clean *O*-debenzylation to afford their parent lactams **10** and **243** in excellent 96% and 97% yields. (Scheme 2.3.9.)




**Scheme 2.3.9.** Hydrogenation of benzyl lactim ethers **241** and **242** to afford their parent lactams **10** and **243**.

## 2.3.6. Attempted alkylation of the *aza*-enolates of benzyl capro and oenantholactim ethers

Repeated attempts to alkylate the *aza*-enolates of benzyl lactim ethers **241** and **242** using conditions that had previously proven successful for the seven membered methyl caprolactim ether **16** were unsuccessful in affording any α-alkyl benzyl lactim ether products **244**, instead affording crude reaction mixtures of several products that could not be separated after exhaustive chromatography. (Scheme 2.3.10.) This was accounted for by the increased reactivity of the benzyloxy fragment of benzyl caprolactim ether **241** that had been observed previously during chromatographic purification. Identical results were recorded for benzyl oenantholactim ether **242**.




**Scheme 2.3.10.** Attempted alkylation of the *aza*-enolates of benzyl lactim ethers **241** and **242**.

As a result attempts to alkylate **241** and **242** shifted to employing alternative conditions, including $^{t}$BuLi, $^{n}$BuLi, KO$^{t}$Bu, NaH, LHMDS, KHMDS and MeLi as well as varying the amount of time allowed for deprotonation at room temperature between 5 and 15 minutes. However, in all these cases all conditions proved unsuccessful in affording the desired α-alkyl products **244** and **245**.

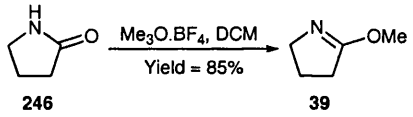
Therefore, while these results clearly demonstrated that hydrogenation of benzyl lactim ethers provided a good route to the formation of large ring size lactams conditions I was unable to identify conditions that would enable their *aza*-enolate to be generated and alkylated in good yield.

## 2.4. Investigation into alkylation of the *aza*-enolate of butyrolactim ether 39

Having identified conditions that would enable the *aza*-enolates of six and seven membered lactim ethers to be alkylated in good yield, attention turned to five membered butyrolactim ether substrates.

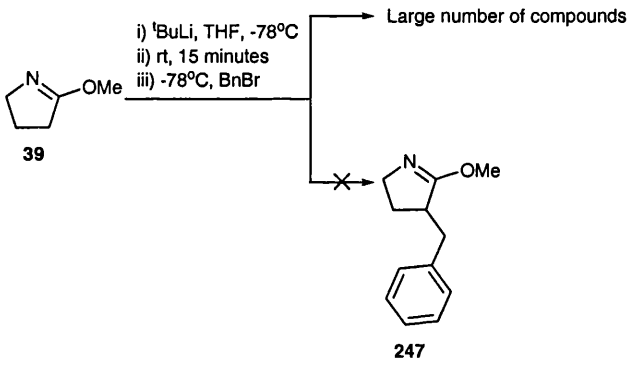
### 2.4.1. Preparation of α-alkyl butyrolactim ethers

The five membered butyrolactim ether **39** was prepared *via* treatment of butyrolactam **246** with $Me_3O.BF_4$ in dichloromethane, as described previously for the six, seven and eight membered lactim ethers, in 85% yield. (Scheme 2.4.1.)



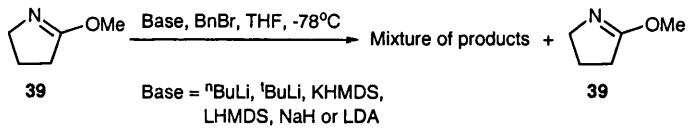

**Scheme 2.4.1.** Preparation of lactim ether **39** from the parent lactam **246**.

Alkylation of the *aza*-enolate of butyrolactim ether **39** did not proceed as expected, since the original conditions developed for the valerolactim series resulted in formation of numerous products in the $^1$H NMR spectra of the crude reaction mixture. This implied that the five membered ring substrate **39** was more reactive than its six membered counterpart **15**, since the valerolactim ether **15** had required 15 minutes at room temperature to be fully deprotonated, whilst the butyrolactim ether **39** was completely destroyed under these conditions. (Scheme 2.4.2.)




**Scheme 2.4.2.** Unsuccessful alkylation of the *aza*-enolate of butyrolactim ether **39**.

In an attempt to reduce the number of side reactions produced in this reaction $^n$BuLi was employed as base at -78 °C, however, once again a large number of products were formed, with extensive purification by column chromatography failing to afford any clean products. Given the number of compounds produced, and the inability to purify any compounds to homogeneity, it was impossible to predict if the desired α-benzyl butyrolactim ether **247** had been formed. At this point a large number of bases including LDA, LHMDS, NaH, KO$^t$Bu and MeLi were screened, all of which returned trace amounts of starting material **39** as well as complex mixtures of products. (Scheme 2.4.3.)




**Scheme 2.4.3.** Unsuccessful alkylation of butyrolactim ether **39**.

Consequently, attention was diverted from attempting to form the α-benzyl butyrolactim ether **247** to discovering the identity of some of these unknown compounds, in the hope that elucidation of their structure would enable an effective *aza*-enolate alkylation protocol to be developed. Upon repeating the reaction with $^{n}$BuLi as base and allyl bromide as electrophile a number of products were once again evident in the $^{1}$H NMR and $^{13}$C NMR spectra of the crude product. However, it became immediately apparent from the $^{1}$H NMR spectrum that an allylated product had been formed in significant yield, which after exhaustive column chromatography afforded a single compound, in 12% isolated yield.

$^{1}$H NMR and $^{13}$C NMR spectroscopic analysis of this unknown compound revealed a structure that contained both a $^{n}$butyl group and an allyl side chain, with no resonance corresponding to a methoxy group. Since the synthetic protocol had involved treatment of butyrolactim ether **39** with excess $^{n}$BuLi, followed by warming to room temperature, recooling to -78 °C and addition of allyl bromide at -78 °C, two structures **248** and **249** were proposed for this unknown product. (Figure 2.4.1.)

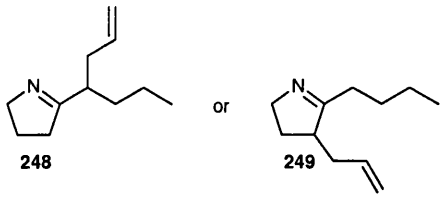



**Figure 2.4.1.** Two possible products arising from treatment of butyrolactim ether **39** with $^{n}$BuLi and allyl bromide.

Analysis of the COSY spectrum of the unknown compound revealed that the methine proton α to the imine functionality was coupled to the methylene protons of the $^{n}$butyl group as well as to the two vinylic methylene protons. (Figure 2.4.2.)

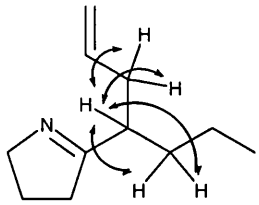
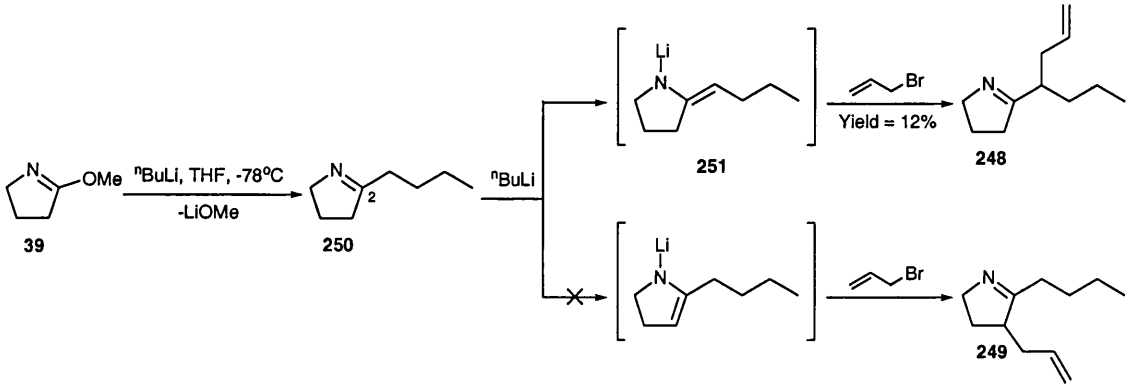



**Figure 2.4.2.** Observed COSY coupling resonances for imine **248**.

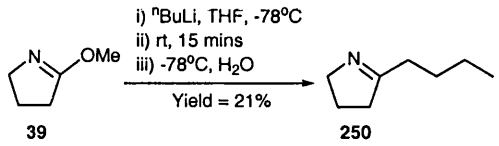
Consequently, the structure of the unknown product was assigned as **248**, whose structural assignment was confirmed from the appearance of eleven resonances in its $^{13}C$ NMR spectrum, and a molecular ion of 166.1590 in its mass spectrum.

Formation of imine **248** therefore occurs by initial nucleophilic displacement of the methoxy unit of butyrolactim ether **39** by $^{n}$BuLi, affording a cyclic imine structure **250**, which is then deprotonated exocyclic to the imine functionality by excess $^{n}$BuLi to afford a lithiated enamine anion **251** that then reacts with allyl bromide. It is noteworthy that no products arising from deprotonation at the alternative endocyclic α-position of imines **248** or **250** within the five membered ring occurs. This may reflect the difficulty involved for these ring α-protons adopting a conformation where they are orthogonal to the imine functionality, due to ring strain within the five membered ring. This contrasts with the exocyclic α-methylene protons, which can easily adopt a conformation where they are orthogonal to the imine functionality *via* free rotation of the butyl fragment around its $C_2$-$C_4H_{11}$ bond. (Scheme 2.4.4.)




**Scheme 2.4.4.** Mechanism accounting for the observed *exo*-alkylation of imine **248**.

In order to gain more evidence for this mechanistic pathway the reaction was repeated in the absence of an electrophile in an attempt to isolate the intermediate cyclic imine **250**. Thus, treatment of **39** with $^{n}$BuLi at -78° C in THF followed by warming to room temperature for 15 minutes before recooling to -78 °C, and quenching by addition of water afforded **250** as a crude product in approximately 21% yield after column chromatography.[73] (Scheme 2.4.5.)



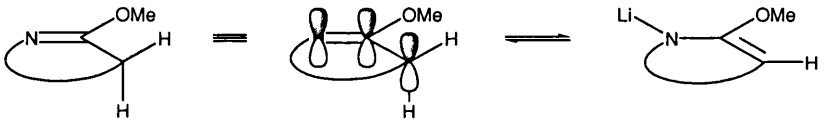

39 250

**Scheme 2.4.5.** Preparation of butyl imine **250** through nucleophilic substitution of the methoxy group of butyrolactim ether **39**.

## 2.4.2. Mechanism of *aza*-enolate formation versus imine formation for lactim ethers

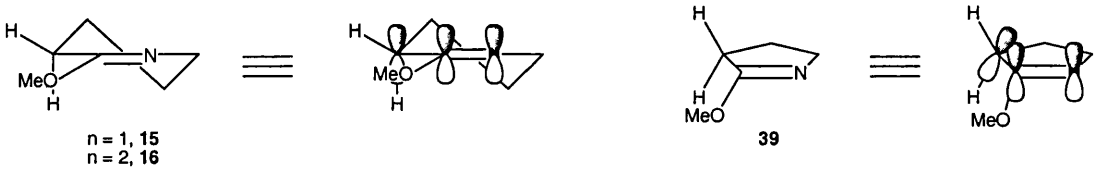
Therefore, it appears from these studies that butryolactim ether **39** cannot be readily deprotonated to afford its corresponding *aza*-enolate intermediate, with the competing nucleophilic displacement reaction occurring in preference. This result obviously contrasts with the observed results for the six and seven membered analogues, whose *aza*-enolates are readily generated at room temperature and alkylated at their α position with no evidence of any imine species having been formed. It was proposed that these contrasting results might be explained by considering the mechanism and stereoelectronic requirements of *aza*-enolate formation.

It is proposed that in order to understand the conditions required for the formation of the *aza*-enolate intermediate the orbital alignment of the α-hydrogen atoms of the lactim ether relative to its imidic π orbitals must be considered. In order for deprotonation to occur the α-C-H σ orbital must be aligned in a coplanar fashion with the π orbitals of the imidic bond thus enabling transfer of electron density through the π-system onto the nitrogen atom of the resultant *aza*-enolate. (Scheme 2.4.6.)



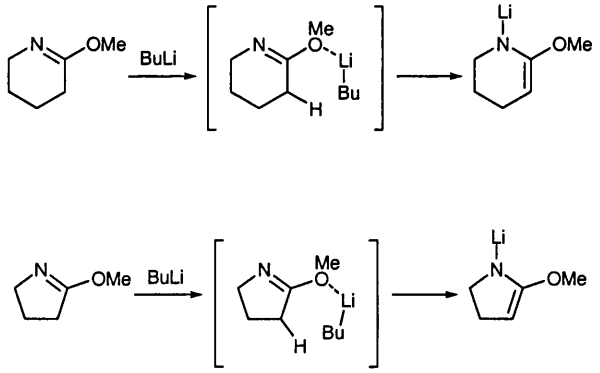

**Scheme 2.4.6.** Proposed essential orbital alignment of a lactim ether during deprotonation.

It is possible that for six and seven membered lactim ethers **15** and **16** that there is sufficient conformational flexibility within the ring system for this orbital alignment to occur, whilst in the case of the five membered lactim ether **39** the ring structure is comparatively rigid and unable to readily achieve the desired orbital overlap. (Scheme 2.4.7.)



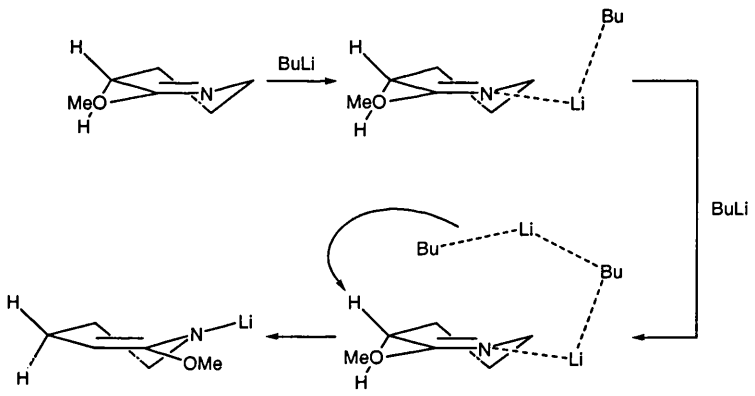

**Scheme 2.4.7.** Orbital alignments of valerolactim ether **15** compared with butyrolactim ether **39**.

Furthermore it is proposed that the coordinative interactions between the base and the lactim ether prior to deprotonation must also be considered. Lactim ethers contain two centres of Lewis basicity, the imidic nitrogen atom and the oxygen atom of the alkyloxy unit, both of which are available for coordination to the lithium counterion of the alkyl lithium base. Coordination of the alkyl lithium to the oxygen atom of the alkyloxy moiety would result in conformationally flexible complexes for both five and six membered lactim ethers which would lead to the same reaction products for both substrates. Since this was not observed it was reasoned that any coordination of the base to the lactim ether substrates was occurring through their imidic nitrogen atoms. (Scheme 2.4.8.)




**Scheme 2.4.8.** Coordination of organolithium species to the alkoxy units of butyro **39** and valerolactim ethers **15**, leading to *aza*-enolate formation.

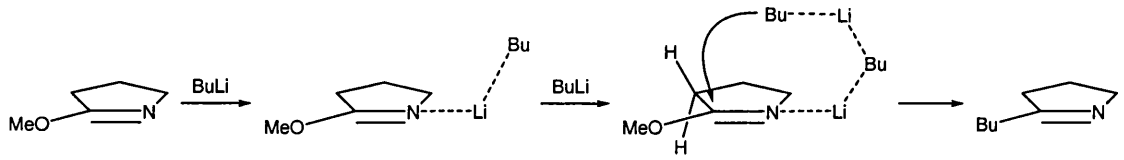
It was speculated therefore, that for valerolactim ether **15** coordination of the lithium counterion to the nitrogen atom of the lactim ether occurs followed by formation of a secondary complex involving coordination of a second equivalent of organolithium reagent. This would afford an assembly that would be capable of bridging to the α-protons of the lactim ether substrate, thus enabling deprotonation of the substrate to occur. (Scheme 2.4.9.)




**Scheme 2.4.9.** Coordination of two equivalents of BuLi to valerolactim ether **15** to effect deprotonation and afford the *aza*-enolate.

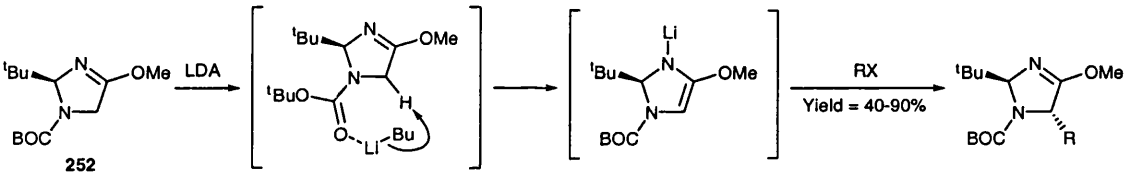
For the case of butyrolactim ether **39** a similar *N*-coordination pathway for the $^{n}$BuLi could occur, however the five membered ring structure is sufficiently rigid, and the bond angles sufficiently acute, to prevent deprotonation from occurring. Therefore the inability of two alkyl lithiums to bridge to the α-protons of butyrolactim ether **39** results

in the nucleophilic addition pathway predominating to afford the observed imine species. (Scheme 2.4.10.)



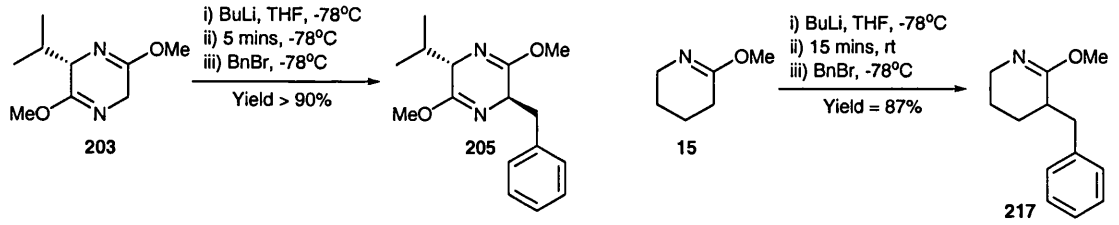

**Scheme 2.4.10.** *N*-coordination of two equivalents of $^{n}$BuLi to butryolactim ether **39** results in nucleophilic substitution to afford imine **248.**

It should be noted that Seebach *et al.* have reported that the *aza*-enolate of a highly functionalised five membered lactim ether **252** could be alkylated in high d.e.[133] However, in this case the proposed mechanism for deprotonation is likely to involve coordination of the organolithium base to the oxygen atom of the carbamate protecting group which would serve to facilitate deprotonation. (Scheme 2.4.11.)



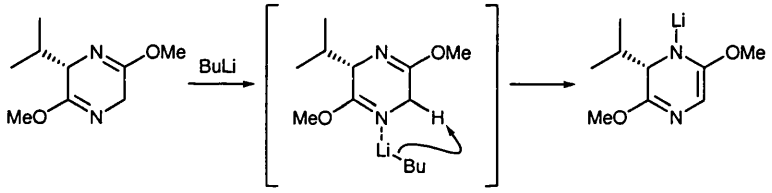

**Scheme 2.4.11.** Seebach's deprotonation of a complex butyrolactim ether substrate and subsequent alkylation.

Indeed, comparison of the conditions required to deprotonate valerolactim ether **15** with those required to generate the *aza*-enolate of Schöllkopf's *bis*-lactim ether **203** illustrate the importance of lithium coordination in these reactions, Therefore, formation of the *aza*-enolate of valerolactim ether **15** requires the use of $^{t}$BuLi at room temperature for 15 minutes whilst deprotonation of the *bis*-lactim ether **203** occurs in 5 minutes with $^{n}$BuLi at -78 °C.[117] (Scheme 2.4.12.)




**Scheme 2.4.12.** Formation of the *aza*-enolates of Schöllkopf's *bis*-lactim ether **203** and valerolactim ether **15** under widely different reaction conditions.

Whilst the p$K_a$ of *bis*-lactim ether **203** is considerably lower than the p$K_a$ of valerolactim ether **15**, both $^{n}$BuLi and $^{t}$BuLi are extremely strong bases that can readily deprotonate both substrates. Therefore, it is likely that the increased reactivity of *bis*-lactim ether **203** is a consequence of the ability of the lone pair of electrons of the nitrogen atom that is proximal to the methylene group being able to coordinate to the lithium counterion of $^{n}$BuLi, and thus facilitate deprotonation at its ortho position. (Scheme 2.4.13.)




**Scheme 2.4.13.** *N*-coordination of $^{n}$BuLi to Schöllkopf's *bis*-lactim ether **203** results in rapid deprotonation to afford an *aza*-enolate **204**.

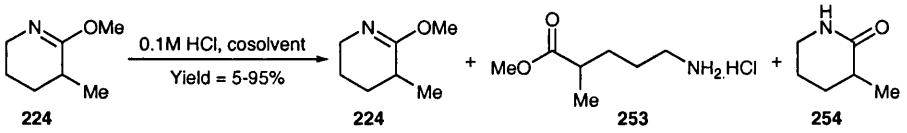
Therefore in conclusion, conditions have been established that enable well behaved, highly nucleophilic *aza*-enolate of six and seven membered lactim ethers to be generated, which react with electrophiles to afford α-alkyl lactim ethers in good yield. The corresponding *aza*-enolate alkylation reactions of five membered lactim ethers were unsuccessful, instead affording products arising from nucleophilic attack of the alkyl lithium species employed as base.

# 2.5. Preparation of a range of α-alkyl amino esters hydrochloride salts

With a range of α-alkyl lactim ethers **217, 224-229** in hand, the next step was to identify conditions that would enable clean hydrolysis of the α-alkyl lactim ethers to their corresponding α-alkyl ω-amino esters.

## 2.5.1. Hydrolysis of α-alkyl valerolactim ethers

α-methyl valerolactim ether **224** was initially selected as a model compound to optimise conditions for this type of hydrolysis reaction as it exhibited a diagnostic doublet resonance for its methyl group in its $^1$H NMR spectrum at δ 1.07. (Scheme 2.5.1.) Hydrolysis of the lactim ether functionality has been reported to be a facile process that proceeds under very mild conditions,[24, 48-50] however, it was found that treatment of α-methyl lactim ether **224** with 0.1M $HCl_{(aq)}$ failed to afford the desired amino ester salt **253** in a good yield. It was proposed that lactim ether **224** was only sparingly soluble in aqueous solution and as a result it was decided to employ an organic co-solvent in the hydrolysis reactions. Initial efforts concentrated on commonly used water miscible organic solvents to increase the solubility of the lactim ether in the aqueous media, however all these homogenous mixed solvent systems failed to afford quantitative conversion to the desired ω-amino ester. Remarkably however, it was found that the use of $CHCl_3$ as an immiscible cosolvent with 0.1M $HCl_{(aq)}$ was successful in affording the desired ω-amino ester **253** in excellent yield.




224 224 253 254

**Scheme 2.5.1** Hydrolysis of α-methyl valerolactim ether **224**.

| Entry | Co-solvent | % yield of lactim ether | % yield of amino ester | % yield of amide |
|---|---|---|---|---|
| 1 | None | 34 | 60 | 6 |
| 2 | THF | 60 | 27 | 13 |
| 3 | MeCN | 86 | 12 | <5 |
| 4 | Acetone | <5 | 30 | 69 |
| 5 | $MeNO_2$ | 92 | 8 | 0 |
| 6 | MeOH | 94 | 5 | <5 |
| 7 | $CHCl_3$ | 0 | >95 | 0 |

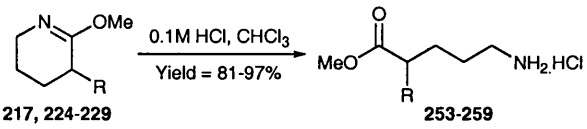
**Table 2.5.1.**

Therefore, a simple hydrolytic protocol was developed in which the lactim ether **224** was dissolved in $CHCl_3$ before addition of 0.1M $HCl_{(aq)}$ and the reaction mixture allowed to stir vigorously overnight, before the solvents were removed *in vacuo* to afford the amino ester hydrochloride salt in 92% yield. Whilst resolution problems were encountered when the $^1H$ NMR spectrum of **253** was run in $CDCl_3$ it was found that employing $d_4$-methanol as solvent resulted in a clean well resolved $^1H$ NMR. The $^1H$ NMR spectrum of **253** revealed a doublet at δ 1.07 (*J* 7.0 Hz), and a new methyl ester singlet at δ 3.56, whilst the $^{13}C$ NMR spectrum showed seven peaks, including a resonance at 178.6 ppm corresponding to an ester carbonyl, as well as the expected molecular ion of 146.1172 in its mass spectrum. Interestingly, IR data of **253** revealed an absorption at 1643 $cm^{-1}$ in a region more normally associated with an amide bond, which may have resulted from the amino ester spontaneously cyclising on the KBr disc when the solvent was removed.

## 2.5.2 Preparation of a range of α-alkyl ω-amino ester hydrochloride salts

These optimised cleavage conditions were then applied to the hydrolysis of the remaining mono substituted lactim ethers **217**, **225-229**, which cleanly afforded their corresponding α-alkyl ω-amino esters **253-259** in good yield as their hydrochloride salts. (Scheme 2.5.2.) It was found that the stability of the α-alkyl lactim ethers

increased as the bulk and lipophilicity of the α-alkyl group increased, proving most problematic for the $^{i}$butyl **258** and $^{i}$propyl lactim ether **259**, which required 0.3M HCl solution for complete hydrolysis to occur.




**217, 224-229** **253-259**

R = Benzyl, allyl, propargyl, ethyl, $^{t}$butyl and $^{i}$propyl

**Scheme 2.5.2.** Hydrolysis of α-alkyl valerolactim ethers **217, 224-229**.

| Entry | Alkyl group | % yield | $\delta_H$ α-H | $\delta_H$ -C*H*$_2$NH$_2$.HCl | $CO_2Me$ |
|---|---|---|---|---|---|
| 1 | Me | 92 | 2.41 | 2.80 | 3.56 |
| 2 | Bn | 95 | 2.7 | 2.58-2.87 | 3.48 |
| 3 | Allyl | 90 | 2.47-2.58 | 2.93 | 3.67 |
| 4 | Propargyl | 97 | 2.52 | 2.81 | 3.60 |
| 5 | Ethyl | 81 | 2.19-2.33 | 2.83 | 3.60 |
| 6 | $^{i}$Butyl | 91 | 2.41 | 2.76-2.85 | 3.59 |
| 7 | $^{i}$Propyl[4] | Quantitative | 2.47-2.56 | 3.18-3.39 | 3.81 |

**Table 2.6.2.**

All compounds were isolated and characterised demonstrating physical and spectroscopic data consistent with the formation of the α-alkyl ω-amino methyl ester hydrochloride salts.( Figure 2.5.1.)

[4] Run in $D_2O$ as an NMR experiment

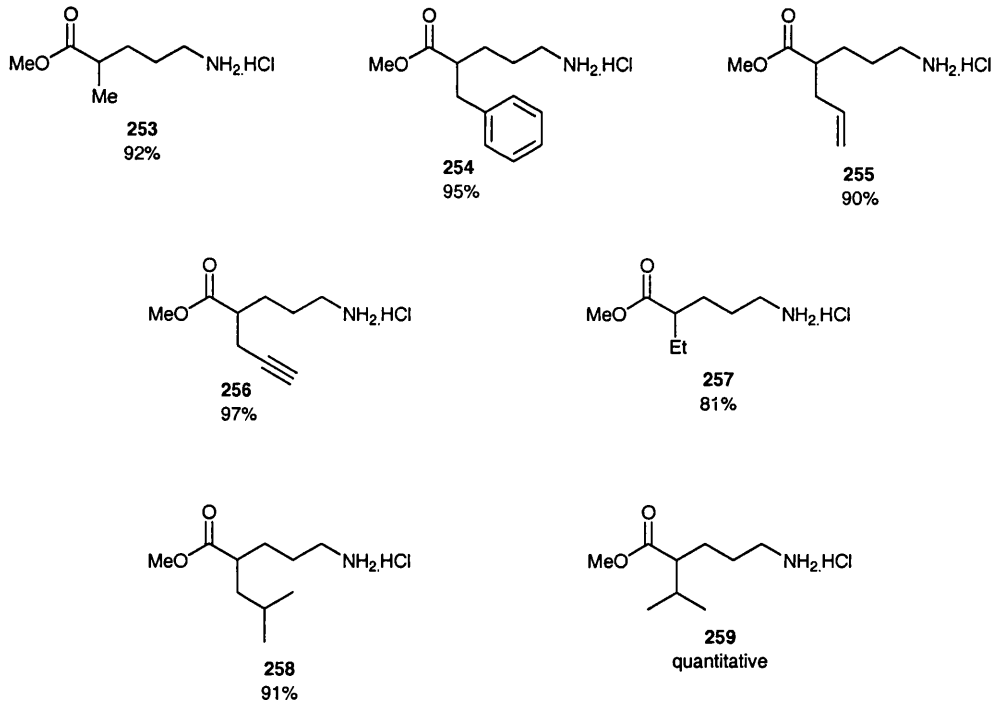



**Figure 2.5.1.** The range of α-alkyl ω-amino ester hydrochloride produced.

It was found that α-benzyl and α-allyl caprolactim ethers also readily underwent hydrolysis under these conditions to afford the corresponding α-alkyl ω-amino esters in 89 and 87% yields respectively. Neutralisation afforded the free amino esters, which were fully characterised and demonstrated spectroscopic and physical data consistent with the formation of α-alkyl caproamino esters.

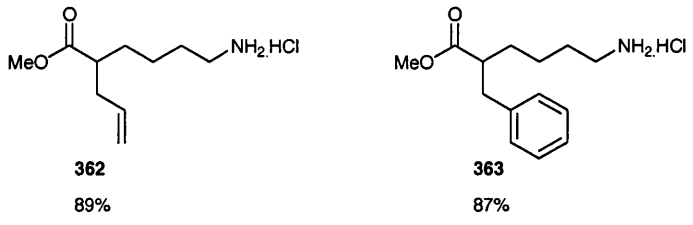
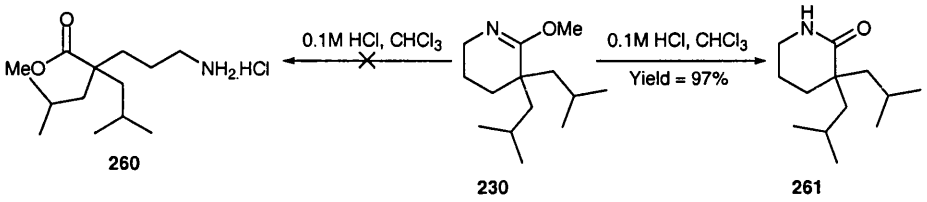



**Figure 2.5.2.** The α-alkyl ω-amino ester hydrochlorides produced from the corresponding α-alkyl capro lactim ethers.

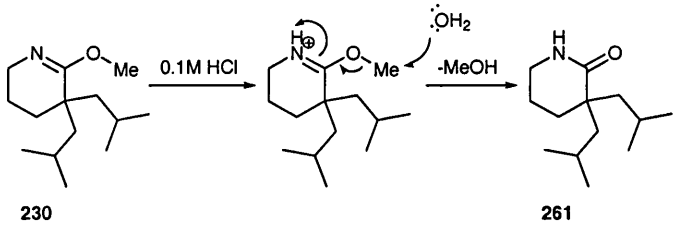
## 2.5.3. Direct formation of α,α-alkyl valerolactams

Attempted hydrolysis of the α,α-di$^{i}$butyl valerolactim ether **230** under these conditions did not result in formation of the expected α-alkyl ω-amino ester **260**, but instead resulted in clean formation of the corresponding α,α-dialkyl valerolactam **261** in quantitative yield. (Scheme 2.5.3.)




**Scheme 2.5.3.** Direct conversion of α,α-di$^{i}$butyl valerolactim ether **230** to α,α-di$^{i}$butyl valerolactam **261** under acidic conditions.

The direct formation of lactam **261** under these conditions was remarkable since ω-amino ester hydrochloride salts normally require neutralisation to its free amine before cyclisation can occur. It was therefore proposed that formation of **261** had occurred *via* a different mechanism, involving protonation of the imine functionality of lactim ether **230**, followed by nucleophilic attack of water at the methyl group of the methoxy group. This pathway would be favoured by the presence of the tertiary α-carbon of **230** which would sterically block nucleophilic attack of the incipient water nucleophile at the imine carbon atom, thus preventing formation of the α-alkyl ω-amino ester. (Scheme 2.5.4.)

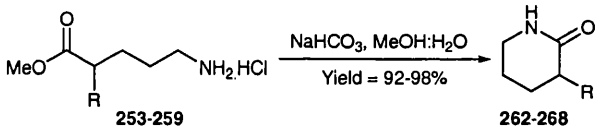



**Scheme 2.5.4.** Mechanism for the formation of α,α-di$^{i}$butyl valerolactam **261** from parent lactim ether **230**.

Indeed, it is likely that the α-alkyl lactams by-products observed previously during optimisation of the hydrolysis reactions of α-methyl valerolactim ether **224** were probably formed *via* this nucleophilic cleavage pathway. (Scheme 2.5.1. and Table 2.5.1.)

## 2.5.4. Preparation of α-alkyl valerolactams

Attention then turned to identifying conditions that would enable facile cyclisation of the α-alkyl ω-amino esters to afford their corresponding α-alkyl valerolactams. Attempts to cyclise the hydrochloride salt of α-methyl ω-amino ester **253** *via* treatment with a methanolic suspension of sodium hydrogencarbonate were unsuccessful. However, repeating this transformation using sodium hydrogencarbonate in a mixed solvent of methanol and water (85:15) afforded a quantitative yield of the desired α-methyl lactam **262**. Applying these conditions to the other ω-amino esters **254-259** also resulted in the formation of their corresponding lactams **263-268** in universally high yields. (Scheme 2.5.5.)




**253-259** **262-268**

R = Benzyl, allyl, propargyl, ethyl, $^{t}$butyl and $^{i}$propyl

**Scheme 2.5.5.** Preparation of α-alkyl valerolactams **262-268** from the corresponding amino ester hydrochloride salt **253-260**.

| Entry | Alkyl group | $\delta_H$ α-*H* | $\delta_H$ C*H*$_2$NH | $\nu_{max}$(C=O) | % yield |
|---|---|---|---|---|---|
| 1 | Methyl | 2.27 | 3.19 | 1665 | 94 |
| 2 | Benzyl | 2.48 | 3.17-3.25 | 1642 | 95 |
| 3 | Allyl | 2.35 | 3.20-3.26 | 1661 | 98 |
| 4 | Ethyl | 2.33-2.43 | 3.23-3.29 | 1670 | 92 |
| 5 | Propargyl | 2.04-2.16 | 3.11-3.19 | 1658 | 92 |
| 6 | $^i$Butyl | 2.13-2.26 | 3.13-3.22 | 1636 | 93 |
| 7 | $^i$Propyl | 2.30 | 3.03-3.19 | 1632 | 94 |

**Table 2.5.3.**

Therefore, conditions have been established that enable α-alkyl lactims to be hydrolysed to their corresponding α-alkyl ω-amino esters, and subsequently cyclised to the α-alkyl lactams in good overall yield.

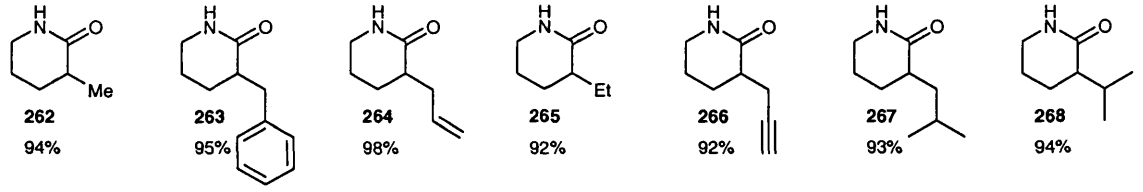



**Figure 2.5.3.** The range of α-alkyl valerolactams **262-268** produced

## 2.6. Summary

This chapter has described detailed investigations into the alkylation of *aza*-enolates of butyro, valero, capro and oenantholactim ethers. It was found that *aza*-enolates of valero and caprolactim ethers readily undergo alkylation with a wide range of electrophiles to afford a range of α-alkyl compounds in good yield. Limitations of this methodology were discovered using five and eight membered lactim ethers as substrates, since competing nucleophilic substitution of the alkyloxy substituent occurs to afford the corresponding imine. α-alkyl lactim ethers could be hydrolysed under mild

conditions to afford the corresponding α-alkyl ω-amino esters, which in turn could be cyclised to afford α-alkyl lactams in excellent yield.

While this approach represents an excellent synthetic route to this class of α-alkyl ω-amino esters and α-alkyl lactams, most biologically active compounds are required in enantiopure form, thus expansion of the methodology to include the formation of enantiopure lactim ethers represents a desirable arena of research. I was therefore interested in applying this methodology to the preparation of α-alkyl ω-amino esters and α-alkyl lactams in enantiopure form, and my attempts to realise the goal using with a chiral auxiliary or a chiral ligand approach are described in the next chapter.

# Chapter 3

# Results and discussion

# Asymmetric alkylation strategies for the alkylation of *aza*-enolates of lactim ethers

# Chapter 3. Asymmetric alkylation of *aza*-enolates of lactim ethers

## 3.1. Introduction

The preceding chapter described the development of novel methodology for the synthesis of α-alkyl ω-amino acids and α-alkyl lactams through the alkylation of the *aza*-enolate of the corresponding lactim ether. All of the target compounds described contain single stereogenic centres and were prepared in racemic form. However, there is an increasing demand for the synthesis of enantiopure compounds for incorporation into libraries of drug like molecules, and as a consequence attention turned towards the development of an asymmetric variant of the previously described *aza*-enolate methodology.

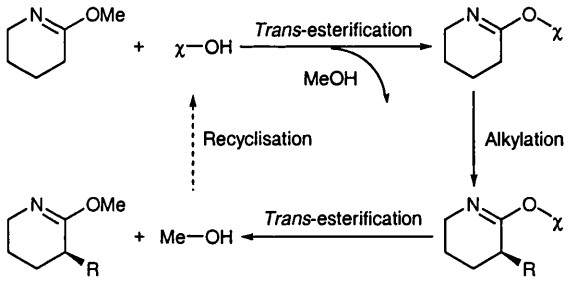
### 3.1.1. A chiral auxiliary approach

Initial attempts were directed towards the development of a three step chiral auxiliary strategy approach for the asymmetric synthesis of enantiomerically pure lactim ethers, according to the protocol described in Scheme 3.1.1. The strategy proposed would involve the following three step protocol:

- Introduction of the chiral auxiliary fragment into the lactim ether skeleton *via* a transesterification reaction

- Formation of the *aza*-enolate of the chiral lactim ether, with subsequent asymmetric alkylation to ideally afford a diastereomerically pure α-alkyl lactim ether

- Removal of the chiral auxiliary fragment *via* transesterification with a simple alcohol to afford enantiomerically pure lactim ethers capable of further transformation to enantiopure α-alkyl ω-amino esters, or α-alkyl lactams.




**Scheme 3.1.1.** Overview of the proposed chiral auxiliary strategy for the formation of enantiopure α-alkyl lactim ethers.

## 3.1.2. Synthesis of enantiopure α-alkyl valerolactim ethers

This chapter of the thesis describes attempts to develop methodology for the asymmetric synthesis of enantiomerically pure lactim ethers that can be easily converted into enantiopure α-alkyl lactams or α-alkyl ω-amino esters. Consequently a brief discussion of the current strategies used for the production of this type of enantiopure compounds now ensues.

## 3.1.3. Biological relevance of enantiopure α-alkyl lactams and α-alkyl ω-amino esters

In recent years many groups have become interested in the pharmacological properties of long chain amino acids and lactams.[110, 134] Various reports have demonstrated their use as potential pharmacophores for drug discovery, or as peptide mimics capable of affording tertiary structures that are more stable than those found in conventional peptides derived from α-amino acids.

For example, 4-aminobutanoic acid **269** is an inhibitory neurotransmitter in the mammalian nervous system, associated with several neurological disorders such as Parkinson's disease, whilst epilepsy has been implicated with its deficiency. As a consequence several enantiopure analogues of **269** have been synthesised that demonstrate a broad spectrum of pharmaceutical activity.[135] (Figure 3.1.1.)

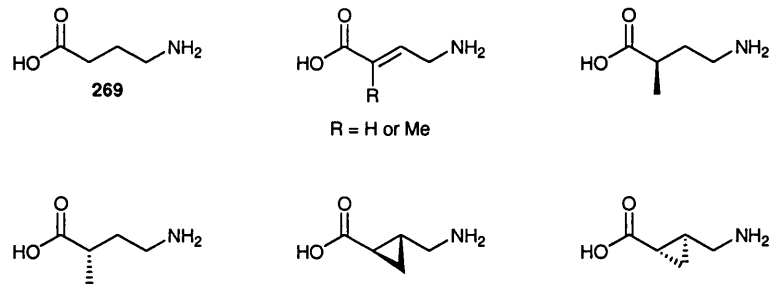



**Figure 3.1.1.** 4-aminobutanoic acid **269** and some related analogues.

In 2003 Seebach *et al.* reported the synthesis of a dipeptide derived from two γ-amino acids **270** as a model for βII' turns of an α-peptide as part of research into the affinities of long chain amino acid peptides for human somatostatin receptors $hsst_1$.[110] The author showed that the secondary *N*-methyl amide forms a stable hydrogen bond with the napthylamide carbonyl group, thus affording a stable fourteen membered secondary ring structure. (Figure 3.1.2.)

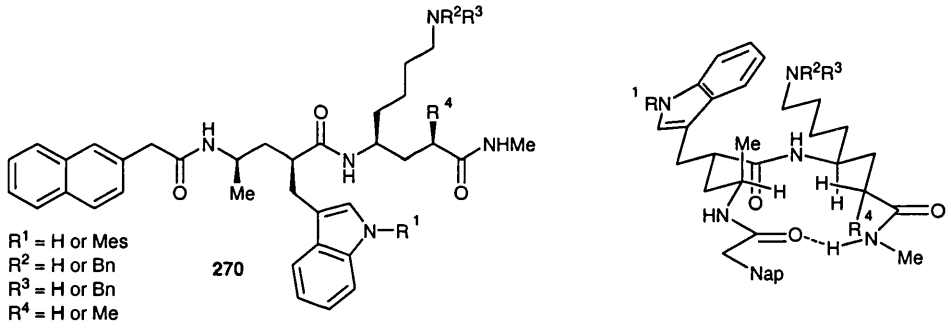
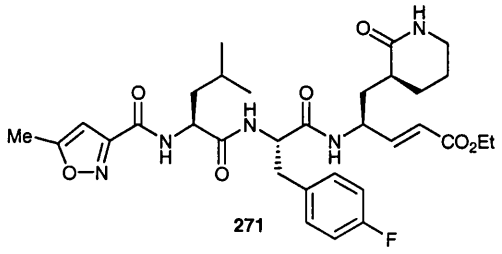



**Figure 3.1.2.** Seebach's peptide mimetic **270** comprised from two γ-amino acids, and the secondary structure proposed to form in solution.

Enantiopure α-alkyl lactams have also been shown to exhibit biological activity. For example, in 1999 Dragovich prepared a protease 3C inhibitor **271**,[136] containing an α-alkyl valerolactam, as a potential therapy for rhinoviruses which are members of the picornavirus family that are the most significant cause of the common cold. (Figure 3.1.3.)



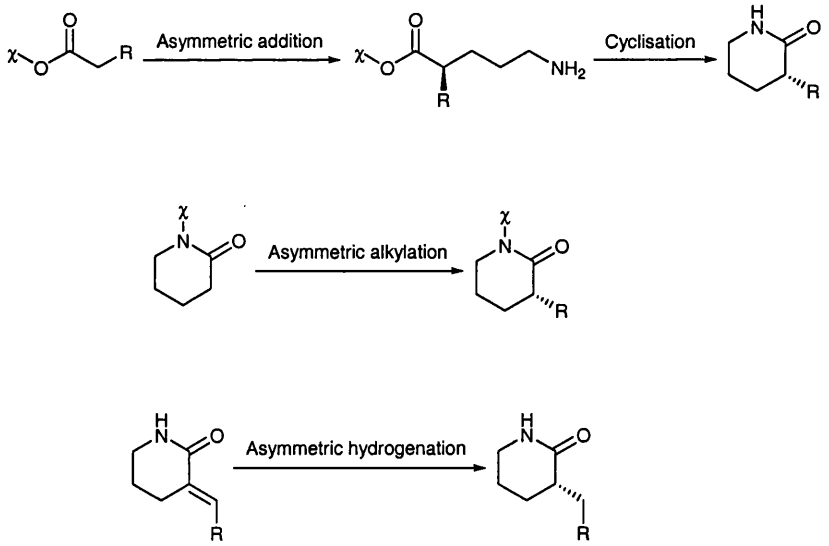

271

**Figure 3.1.3.** Rhinovirus 3C inhibitor **271**.

Therefore, it is clear that there is much current demand for efficient protocols for the asymmetric synthesis of both class of compound.

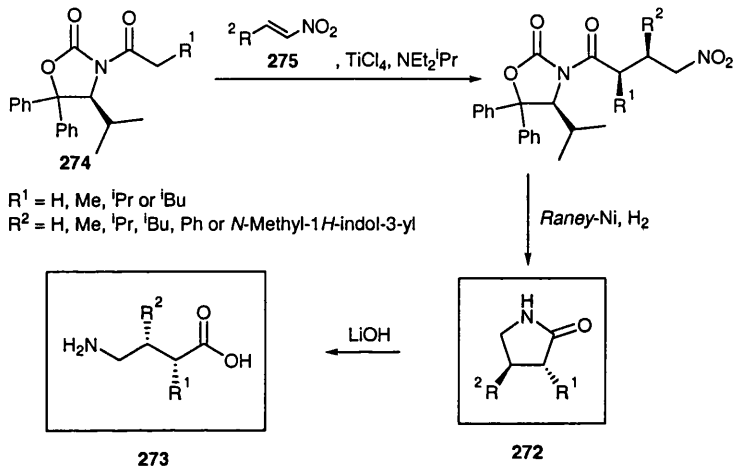
## 3.1.4. Current methodologies for the production of enantiopure α-alkyl lactams and α-alkyl ω-amino esters

Both α-alkyl ω-amino esters and α-alkyl lactams are important synthetic units and as such several approaches have been developed for their asymmetric synthesis. The most commonly used methods involve preformation of the stereogenic centre before ring closure to afford the desired lactam, alkylation of a lactam in the presence of a chiral auxiliary, or asymmetric hydrogenation of an existing lactam containing an α,β-unsaturated side chain. (Scheme 3.1.2.)



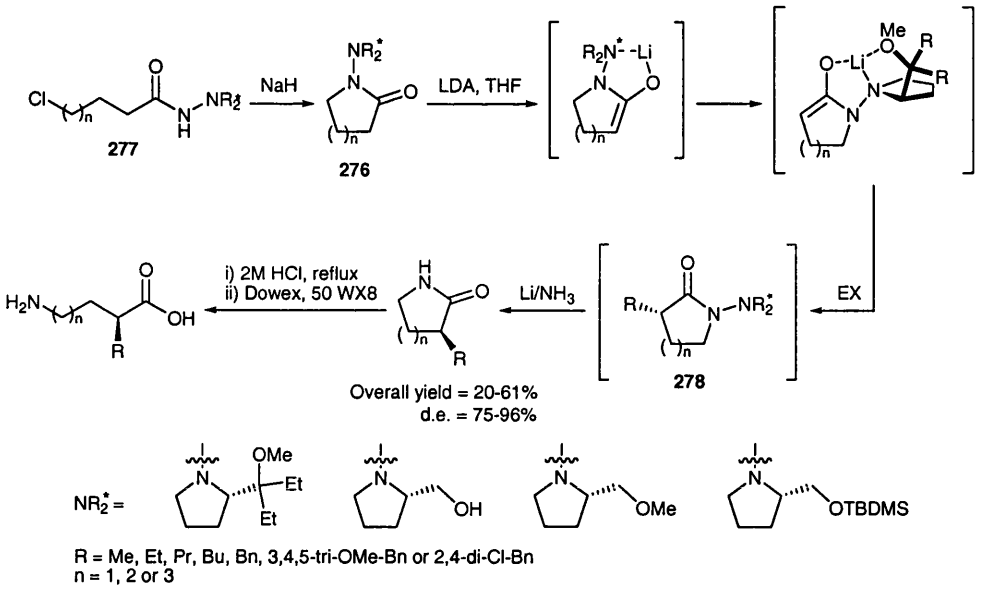

**Scheme 3.1.2.** Current methodology for the production of enantiopure α-alkyl lactams.

For example in 2001 Seebach *et al.* employed a chiral auxiliary approach for the synthesis of a series of α,β-dialkyl butyrolactams **272**, and their corresponding δ-amino acids **273**.[137] They prepared the amino ester core through Michael addition of the titanium enolate of an enantiopure *N*-acyl-oxazolidinone **274** to an α,β-unsaturated nitro acceptor **275**, before reducing the nitro group to an amine that then underwent intramolecular cyclisation with concomitant removal of the auxiliary. Treatment of the resultant α-alkyl lactams **272** with lithium hydroxide allowed formation of the corresponding ω-amino acids **273**, containing two stereocentres in high d.e. (Scheme 3.1.3.)



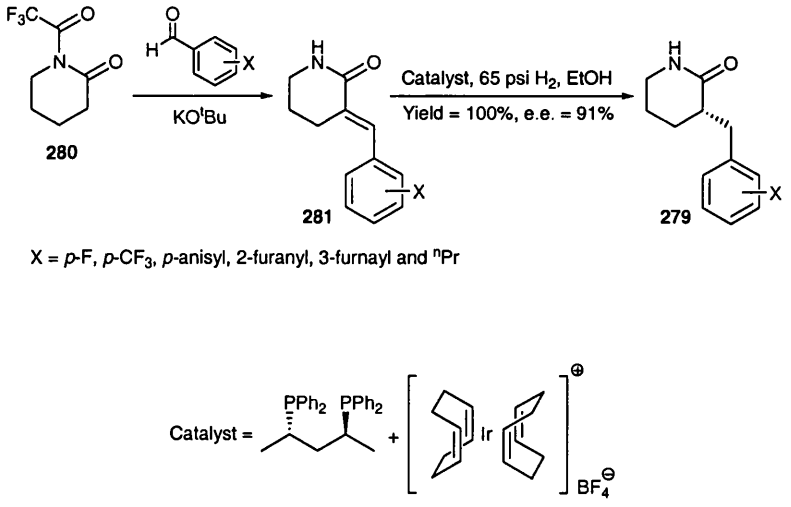

**Scheme 3.1.3.** Preparation of diastereomerically pure α,β-dialkyl butyrolactams **272** through an asymmetric conjugate addition strategy.

Enders *et al.* reported an enantioselective synthesis of α-alkyl butyro, valero and caprolactams *via* alkylation of the enolates of chiral *N*-dialkylamino lactams.[138] The group prepared a series of *N*-amino lactams **276** from their corresponding ω-chloroalkanohydrazides **277**, which were reacted with LDA to afford the desired enolates that were alkylated with a range of electrophiles in high d.e. Subsequent reductive cleavage of the *N-N* bond of **278** using lithium in liquid ammonia afforded a range of lactams in good overall yields (20-61%, over 3 steps), and moderate to good e.e (75-96%). (Scheme 3.1.4.)




**Scheme 3.1.4.** Production of enantiopure α-alkyl lactams using a chiral hydrazine auxiliary **276**.

Asymmetric hydrogenation of α,β-*exo*-unsaturated lactams represents a facile route to enantiopure α-alkyl lactams, that Yue *et al.* have employed this approach for the preparation of a series of 3-benzylpiperidin-2-ones.[139] The group formed the desired 3-alkylidene lactam substrates **279** through aldol reaction of the potassium enolate of *N*-trifluroacetate protected valerolactam **280** with the corresponding aldehyde, followed by *in situ* dehydration of the aldol product **281**. Optimisation studies revealed that asymmetric hydrogenation using 2,4-*bis*(diphenylphosphino)pentane (BDPP) as a chiral ligand for $[(COD)_2Ir].BF_4$ (see entry 1 table 3.1.1.) delivered the desired α-alkyl lactams in high yield and e.e. (Scheme 3.1.5.)




**Scheme 3.1.5.** Production of α-alkyl valerolactams through a catalytic asymmetric hydrogenation strategy.

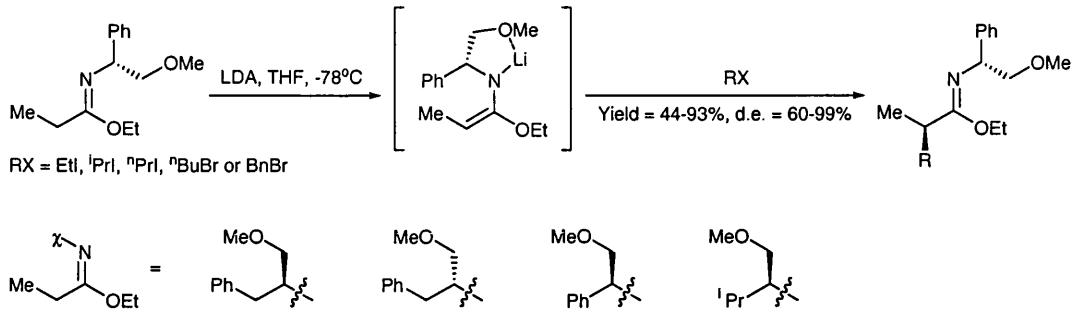
| Entry | Metal precursor | Diphosphine ligand | Conversion % | e.e. |
|---|---|---|---|---|
| 1 | $[(COD)_2Ir].BF_4$ | BDPP | 100 | 91 |
| 2 | $(COD)Ru(MeAl)_2.2HBr$ | BICP | 30 | 85 |
| 3 | $(COD)Ru(MeAl)_2.2HBr$ | $Fe\text{-}PPh_3\text{-}PBu_2$ | 100 | 70 |
| 4 | $(COD)Ru(MeAl) + BF_3/HBF_4$ | Me-Pennphos | 100 | 70 |
| 5 | $[(COD)_2Rh].BF_4$ | BDPP | 100 | 69 |
| 6 | $[(COD)_2Ir].BF_4$ | DIOP | 85 | 66 |

**Table 3.1.1.**

## 3.1.5. Precedent for asymmetric alkylations of *aza*-enolate of imino ethers using chiral auxiliaries for stereocontrol

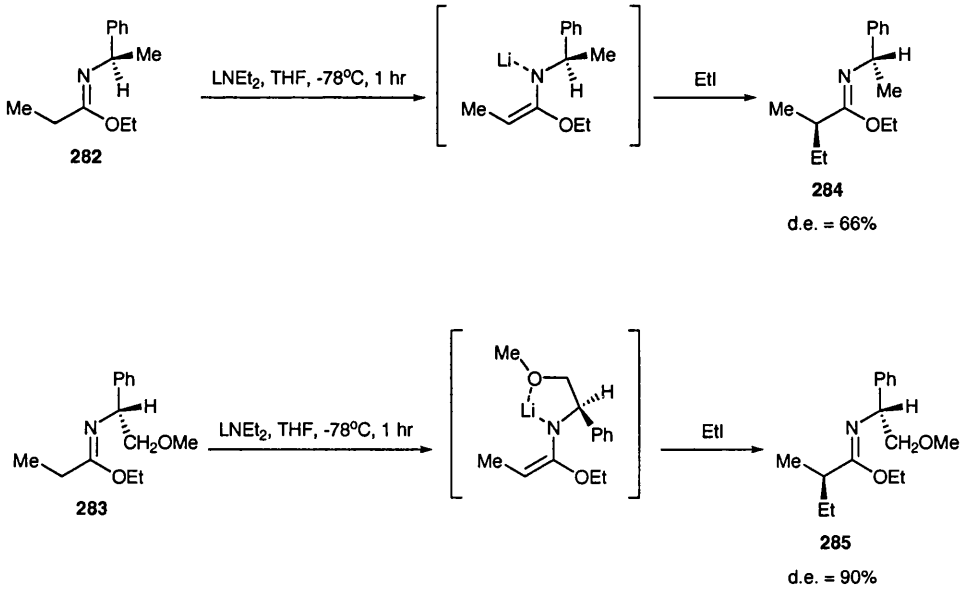
As described, chiral auxiliaries have been employed previously for asymmetric *aza*-enolate alkylation reactions of imino ethers.[120] In 1984 Bergbreiter *et al.* synthesised a series of chiral *N*-α-methoxybenzyl imino ethers **270a-f** as substrates for asymmetric *aza*-enolate alkylation reactions. The group found that deprotonation of these imino ethers in THF at -78 °C afforded intramolecularly chelated *aza*-enolates, which when

treated with electrophiles afforded α-alkyl imino ethers **208-213** in moderate to good d.e. (60-98%). (Scheme 3.1.6.)




**Scheme 3.1.6.** Asymmetric alkylation of a range of imino ethers.

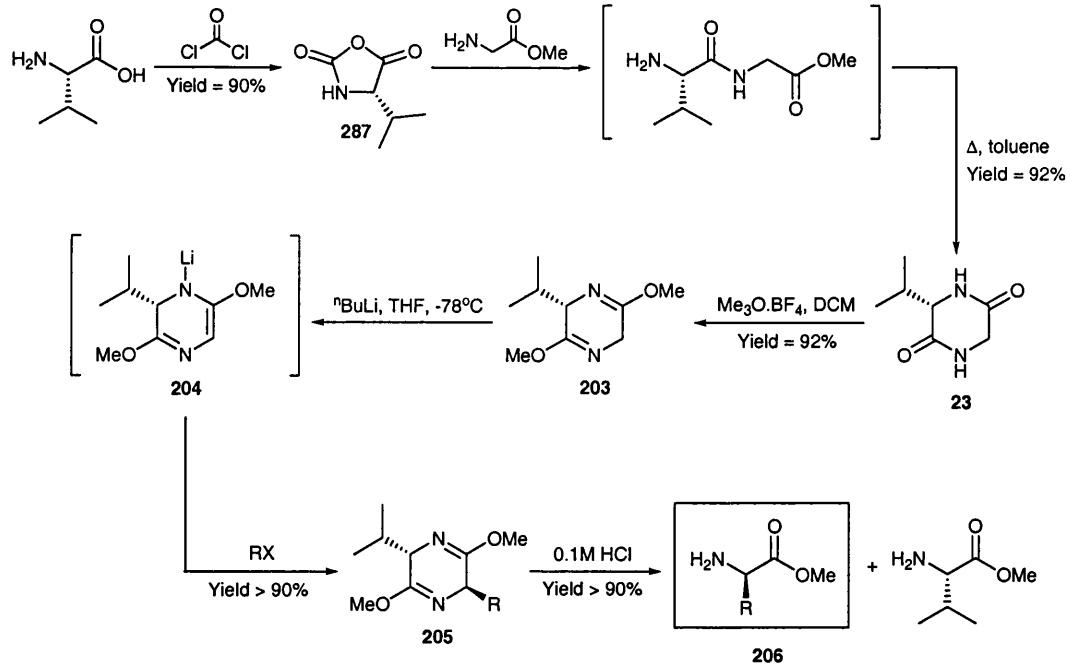
Furthermore, they demonstrated that intramolecular chelation of the methoxy group of the chiral auxiliary in the lithium *aza*-enolate played a large role in the efficient relay of stereochemical information. They synthesised a non-chelating analogue **282** *via* substitution of the methoxy fragment of **283** for a methyl group, which upon treatment with lithium diethylamide in THF at -78 °C afforded the α-alkyl imino ether product **284** as a mixture of two diastereomers in only 66% d.e. compared to the much increased 90% d.e recorded for the methoxy containing species **285**. (Scheme 3.1.7.)




**Scheme 3.1.7.** Alkylation of the *aza*-enolate of chelating **282** and non-chelating **283** imino ethers with loss of diastereomeric control for the non-chelating analogue.

## 3.1.6. Alkylation of Schöllkopf's *bis*-lactim ether chiral auxiliaries

Many reports have appeared in the literature detailing the asymmetric alkylation of *bis*-lactim ethers since Schöllkopf *et al.* first demonstrated their use for the synthesis of enantiopure α-amino esters in 1981.[119] *Bis*-lactim ether chiral auxiliary **203** are formed from the corresponding naturally occurring L-valine from the corresponding diketopiperazine **23**, which in turn was formed in two steps from the Leuch's anhydride of L-valine **287**. They showed that treatment of the *bis*-lactim ether auxiliary **203** with $^{n}$BuLi in THF at -78 °C, afforded the corresponding *aza*-enolate **204** which reacted with an electrophile to afford the *trans*-alkylated auxiliary **205** in high yield (>90%) and d.e. (>95%). Facile hydrolysis of **205** under aqueous acidic conditions then afforded the enantiopure α-alkyl α-amino ester **206** in good yield. (Scheme 3.1.8.)



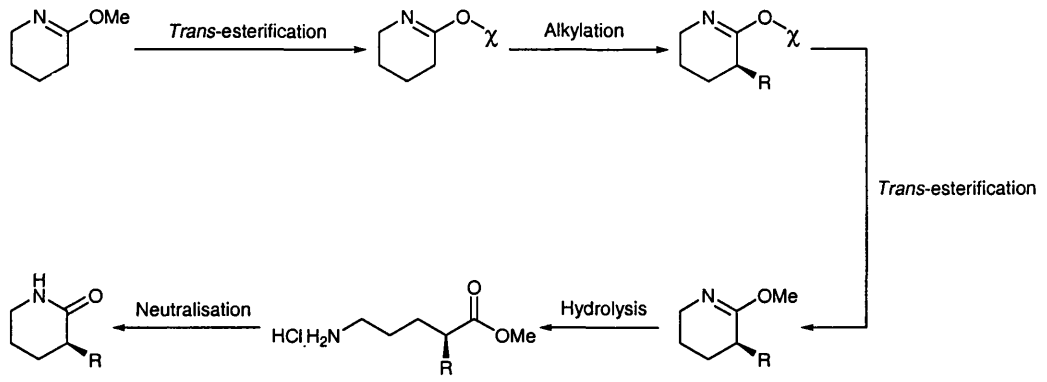

**Scheme 3.1.8.** Overview of the *bis*-lactim ether chiral auxiliary methodology developed by Schöllkopf.

Bergbreiter and Schöllkopf's work clearly demonstrates good precedent for the use of chiral auxiliaries for the enantioselective formation of chiral α-alkyl lactim ethers. However, to date, there remain no reported examples of asymmetric synthesis using simple lactim ether substrates that employ a readily removable chiral auxiliary. Consequently, it was decided to attempt to develop efficient methodology that would enable chiral auxiliaries to be used for stereocontrol in the alkylation of *aza*-enolates of simple lactim ethers.

## 3.1.7. New approach to the synthesis of enantiomerically enriched α-alkyl lactim ethers

In chapter 2 of this thesis it has been shown that *aza*-enolates of valero and caprolactim ethers may be α-alkylated in good yield. Consequently a new route to the synthesis of enantiomerically enriched α-alkyl lactams was proposed in which the lability of the lactim ether alkyloxy bond could be exploited to introduce and remove a chiral auxiliary fragment *via* a transesterification strategy. Deprotonation of the resultant chiral lactim ether would result in an *aza*-enolate which would react with electrophiles

under the control of the chiral auxiliary fragment to generate enantiopure α-alkyl lactim ether, ideally as a single diastereomer. Subsequent removal of the chiral auxiliary fragment *via* a transesterification with methanol, followed by hydrolysis would then afford the desired α-alkyl ω-amino ester or α-alkyl lactams in good yield. (Scheme 3.1.9.)

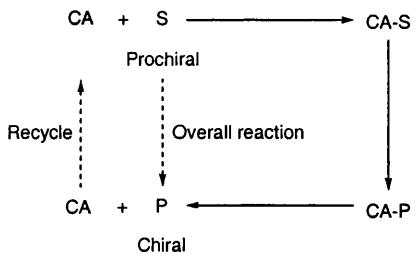



**Scheme 3.1.9.** Alkylation of chiral lactim ethers and further conversion into α-alkyl ω-amino esters or α-alkyl lactams.

Since this approach relies on the use of a chiral auxiliary for stereocontrol a brief discussion of the factors that were considered in choosing suitable chiral auxiliary for asymmetric synthesis now follows.

## 3.1.8. Review of the use of chiral auxiliaries

Chiral auxiliaries represent a facile method for the introduction of new stereocentres into a prochiral molecule. There are many examples where chiral auxiliaries have been used for asymmetric synthesis, however they normally operate in a similar manner. The chiral auxiliary is first attached to a prochiral substrate to generate an enantiopure compound which is then functionalised under the control of the chiral auxiliary to afford a new product containing one or more new stereocentres in high d.e. Purification of this mixture of diastereomers to homogeneity, followed by cleavage of the chiral auxiliary fragment, affords the desired product in enantiopure form and allows the chiral auxiliary to be recycled. (Scheme 3.1.10.)




**Scheme 3.1.10.** Generic overview of the use of chiral auxiliaries for asymmetric synthesis.

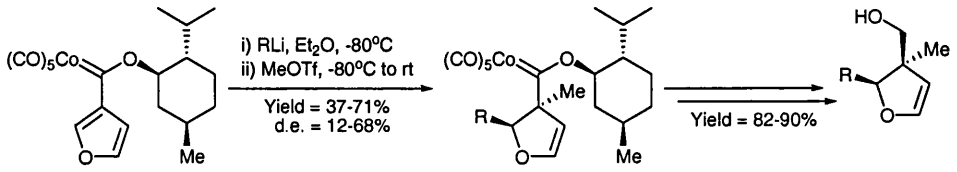
The ideal properties of a chiral auxiliary have been well documented and they should ideally demonstrate the following features:

- Inexpensive enantiopure substrates
- Commercially available
- Both enantiomers are readily available
- Facile attachment of the auxiliary to the substrate
- Applicable to a broad variety of substrates
- Stable under a wide range of reaction conditions
- High and predictable levels of stereoselectivity
- Simple purification of intermediates and products e.g. crystalline intermediates
- Facile cleavage of the auxiliary from the derivatised substrate
- Recyclable and robust

After consideration of the range of commercially available chiral alcohols that were available as chiral auxiliary fragments for my proposed lactim ether transesterification strategy, it was decided to employ a cheap terpene derived alcohol for stereocontrol due to their ready availability from the chiral pool.

(-)-Menthol was selected as the initial auxiliary owing to its immediate availability within the laboratory, its fulfilment of the criteria listed above, and the fact that (-)-menthol has been previously employed as a chiral auxiliary to control facial selectivity for a wide range of asymmetric transformations. For example, in 2003 Barluenga *et al.*

employed (-)-menthol as a chiral auxiliary for the diastereoselective dearomatisation and alkylation of substituted furans.[140]

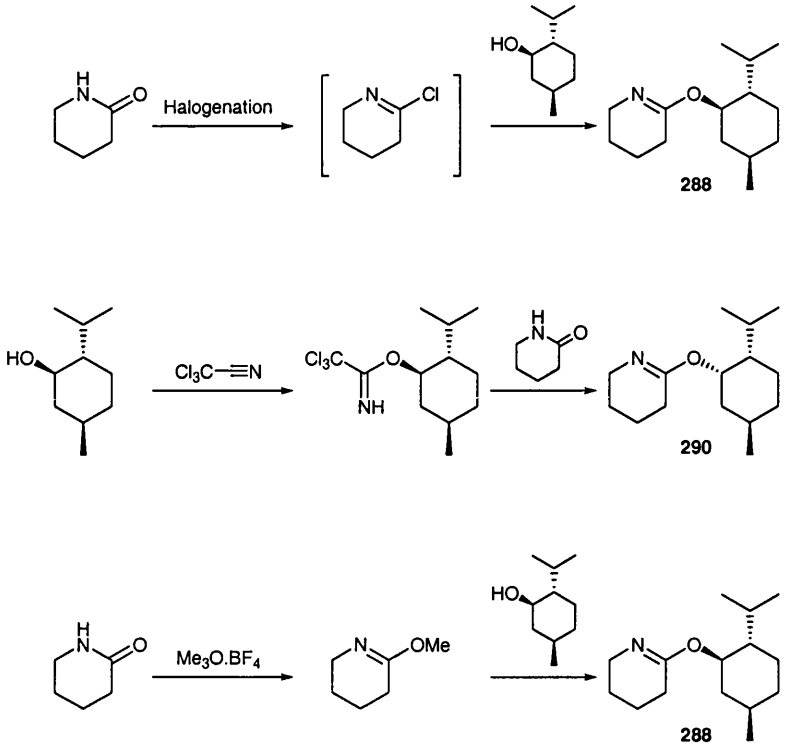



**Scheme 3.1.11.** The employment of (-)-menthol as a chiral auxiliary in the diastereoselective dearomatisation of a furan.

## 3.2. Development of effective asymmetric *aza*-enolate alkylation methodology

### 3.2.1. Preparation of (-)-menthol lactim ether 288

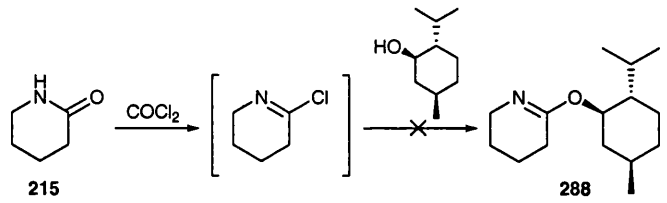
A review of the literature for approaches towards the formation of lactim ethers revealed several methods that were available for the synthesis of a lactim ether containing a menthol chiral auxiliary **288**. Three approaches were initially chosen for investigation; creation of an intermediate iminoyl halide followed by quenching with menthol; the use of a (-)-menthol derived trichloroacetimidate reagent; or introduction of (-)-menthol through a transesterification strategy. (Scheme 3.2.1.)




**Scheme 3.2.1.** Formation of (-)-menthol valerolactim ether **288** and **290** through formation of an iminoyl halide, trichloroacetimidate or transesterification strategy.

## 3.2.2. Attempted formation of a (-)-menthol derived valerolactim ether *via* an iminoyl halide intermediate

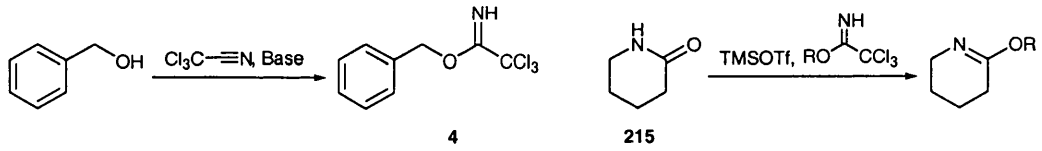
Initial attempts to synthesise chiral lactim ether **288** *via* an iminoyl halide intermediate followed the precedent of Jurczak *et al.*[12] However, attempts to prepare a (-)-menthol lactim ether **288** *via* treatment of valerolactam **215** with phosgene, followed by alcoholysis with (-)-menthol, proved unsuccessful with quantitative return of starting materials. Parallel control reactions employing benzyl alcohol and methyl alcohol, as alternative nucleophiles, were also unsuccessful, once again returning recovered valerolactam **215** as the only product. (Scheme 3.2.2.)




**Scheme 3.2.2.** Attempted formation of **288** through an iminoyl halide strategy.

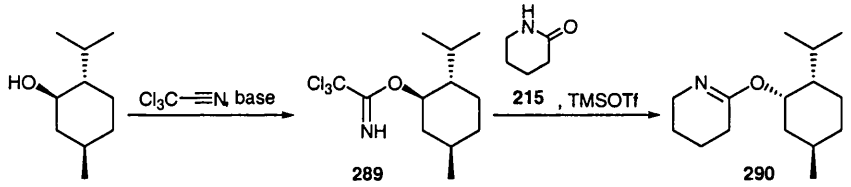
## 3.2.3. Attempted preparation of terpene derived lactim ethers *via* trichloroacetimidate methodology

As described in section 1.4.5. trichloroacetimidate reagents represent a mild and selective reagent for the preparation of lactim ethers. Furthermore, they are relatively easy to prepare through treatment of the desired alcohol with trichloroacetonitrile in a base catalysed Pinner synthesis. No examples of chiral variants of this methodology exist however, despite the synthetic opportunities that this transformation might offer. (Scheme 3.2.3.)




**Scheme 3.2.3.** Attempted formation and employment of trichloroacetimidates for the synthesis of lactim ethers.

It was proposed that the use of (-)-menthol as a nucleophile in the base catalysed Pinner synthesis would afford (-)-menthol trichloroacetimidate **289**, which could then act as a suitable *O*-alkylating source for the formation of (-)-menthol valerolactim ether **290** from valerolactam **215**. It should be noted that reaction of (-)-menthol trichloroacetimidate **289** with a valerolactam **215** in this manner would result in inversion of the stereogenic centre of the resultant chiral lactim ether **290**, *via* an $S_N2$ type process. (Scheme 3.2.3.)

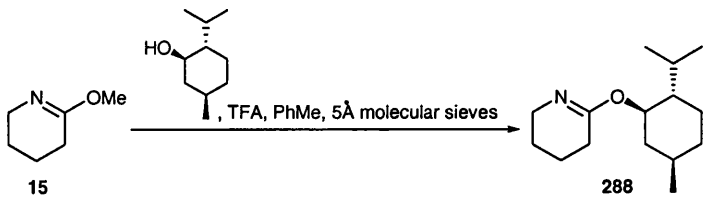



**Scheme 3.2.3.** Formation of menthol derived valerolactim ether **290** through the use of (-)-menthol trichloroacetimidate **289**.

Unfortunately attempts at preparing the required (-)-menthol trichloroacetimidate **289** were unsuccessful, returning only unreacted (-)-menthol. This was a most unexpected result given the success enjoyed previously in the preparation of benzyl trichloroacetimidate **4** which had proceeded readily in high purity and yield, and may reflect the increased steric demand of (-)-menthol as a nucleophile.

## 3.2.4. Preparation of terpene derived lactim ethers *via* transesterification

Given the lack of success in the synthesis of the desired chiral lactim ether from valerolactam **215**, attention then shifted towards an alternative approach, involving transesterification of valerolactim ether **15** with (-)-menthol. It was found that stirring valerolactim ether **15**, (-)-menthol and 1.3 equivalents of TFA in toluene for 16 hours in the presence of 5Å molecular sieves resulted in formation of the desired (-)-menthol lactim ether product **288** in approximately 60% conversion. Purification of the crude reaction product by column chromatography afforded the (-)-menthol derived lactim ether product **288** as a white crystalline solid. (Scheme 3.2.4.)




**Scheme 3.2.4.** Transesterification of valerolactim ether **15** with (-)-menthol.

Examination of $^{1}H$ NMR spectrum of (-)-menthol valerolactim ether **288** revealed diagnostic resonances for the C*H*O position of the terpene fragment at δ 4.61 (td, *J* 10.9 and 4.3 Hz), and the δ methylene protons α to the imidic nitrogen at δ 3.90 (app. ttt, *J* 7.1, 5.7 and 1.1 Hz). Few other $^{1}H$ NMR resonances could be assigned unequivocally due to the overlapping nature of the large number of methylene ring protons in this molecule. Analysis of the $^{13}C$ NMR spectrum was more forthcoming revealing 15 resonances, whilst the infra red spectrum revealed an absorption at 1694 $cm^{-1}$. GC mass spectroscopy did not reveal the expected parent ion of 237, however fragmentation of the parent ion could be readily observed, involving loss of a methyl group at 222, loss of an $^{i}$propyl group at 194, and loss of a (-)-menthol fragment at 100. Accurate mass spectroscopy revealed a parent ion of 238.2168.

Chiral lactim ether **288** was found to be crystalline and was submitted for crystal X-ray analysis, which served to confirm its structure. Thus, the crystal structure revealed that the two ring systems lie orthogonal to each other, with the (-)-menthol cyclohexane ring demonstrating a well defined chair conformation, with the sterically demanding $^{i}$propyl, lactim ether and methyl substituents, all adopting equatorial positions. The lactim ether ring adopts an open book conformation due to the presence of the $sp^2$ carbon and nitrogen atoms of the imidic bond with little evidence of any steric interactions between the terpene and lactim ether ring systems. (Figure 3.2.1.)

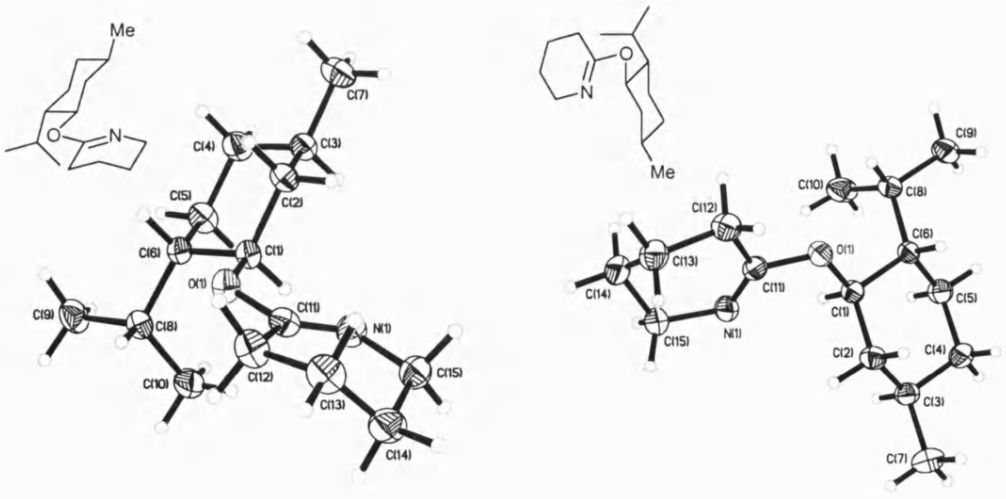
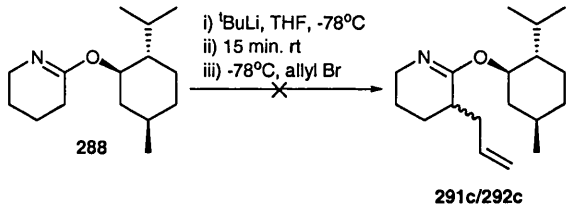



**Figure 3.2.1.** X-ray crystal structure of (-)-menthol valerolactim ether **288**.

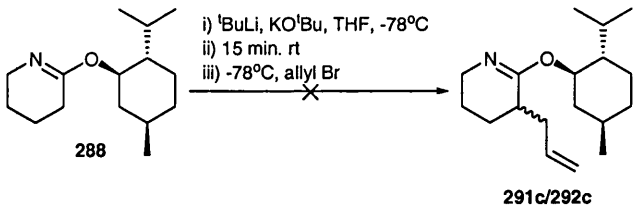
## 3.2.5. Preparation of α-allyl menthol lactim ether 291c and 292c

Allyl bromide was selected as a model electrophile for the *aza*-enolate alkylation studies on (-)-menthol lactim ether **288** due to its excellent reactivity and the fact that the resultant α-allyl (-)-menthol lactim ether product **291c/292c** would display diagnostic resonances in its $^1$H NMR spectrum at δ 4.5-6.0. Initial attempts employed conditions that had previously been shown to be successful for alkylation of the *aza*-enolate of the simple methyl lactim ether analogue. Unfortunately, addition of 1.5 equivalents of $^t$BuLi to **288** in THF at -78 °C, followed by warming to room temperature for 15 minutes before recooling to -78 °C and addition of allyl bromide resulted in recovered starting material with no α-alkyl product **291c/292c** being formed. (Scheme 3.2.5.)



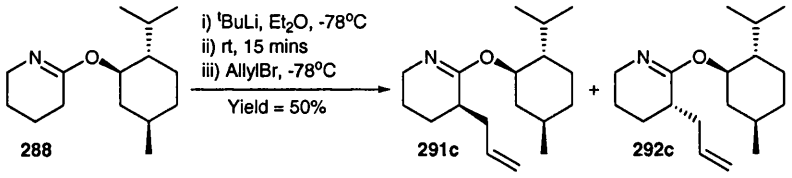

**Scheme 3.2.5.** Attempted alkylation of the *aza*-enolate of (-)-menthol lactim ether **288**.

Having resolved previous problems with sluggish *aza*-enolate alkylation reaction of lactim ethers using Schlosser's base system ($^t$BuLi and KO$^t$Bu in THF at -78 °C), these conditions were also employed however, once again they returned only starting material **288**. (Scheme 3.2.6.)



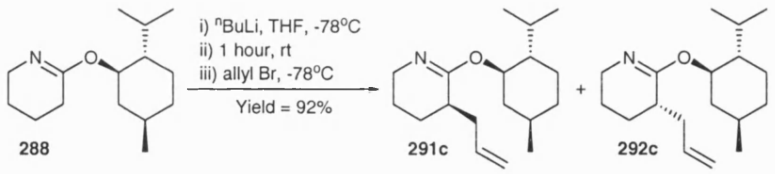

**Scheme 3.2.6.** Attempted alkylation of the *aza*-enolate of **288** using Schlosser's base conditions.

Partial success was observed *via* treatment of lactim ether **288** with 1.5 equivalents of $^{t}$BuLi in $Et_2O$ with subsequent warming to room temperature for 15 minutes before recooling to -78 °C and addition of allyl bromide. This reaction afforded a crude reaction product possessing new allyl containing compounds **291c** and **292c**, as well as 50% recovered starting material **288**. Screening a range of conditions including increasing the concentration of reactants, varying the number of equivalents of base, and varying the reaction times did not drive the alkylation reaction to completion with 40-70% recovered starting material **288** being recovered in each case. As a result an alternative protocol was sought that would provide superior consistency in terms of both yield and reproducibility. (Scheme 3.2.7.)




**Scheme 3.2.7.** Partial alkylation of the *aza*-enolate of **288** using $^{t}$BuLi as base.

It was proposed that the only difference between the (-)-menthol system and the original methyl lactim ether **15** appeared to be the additional steric bulk of the chiral auxiliary fragment, which might be retarding approach of the $^{t}$butyl anion thus preventing deprotonation of the acidic α protons. Bearing in mind this rationale, it was proposed that changing the base from sterically demanding $^{t}$BuLi to $^{n}$BuLi might afford the desired α-allyl (-)-menthol lactim ethers **291c/292c** in superior yield. After a series of optimisation studies it was found that treatment of lactim ether **288** with 2.4 equivalents of $^{n}$BuLi in THF with subsequent warming to room temperature for one hour before recooling to -78 °C, followed by addition of allyl bromide, afforded a quantitative conversion of **288** to its diastereomeric α-allyl (-)-menthol lactim ethers **291c/292c**. (Scheme 3.2.8.)




**Scheme 3.2.8.** Optimised alkylation conditions for (-)-menthol lactim ether **288** using $^{n}$BuLi as base.

$^{1}$H NMR spectroscopic analysis of the optimised reaction of the *aza*-enolate of (-)-menthol lactim ether **288** with allyl bromide appeared to show formation of two diastereomeric products **291c/292c** in a 4:1 ratio. The $^{1}$H NMR spectrum of the mixture of the diastereoisomers was not particularly diagnostic, however partially overlapping resonances of the allylic fragments of the two diastereoisomers could be observed centred at δ 4.90 and δ 4.82 (dm, *J* 10.0 Hz), δ 4.93 and δ 4.79 (dm, *J* 17.0 Hz) and δ 5.62 and δ 5.51 (ddq, *J* 17.0, 10.0, 7.0 Hz) in a 4:1 ratio. (Figure 3.2.2.)

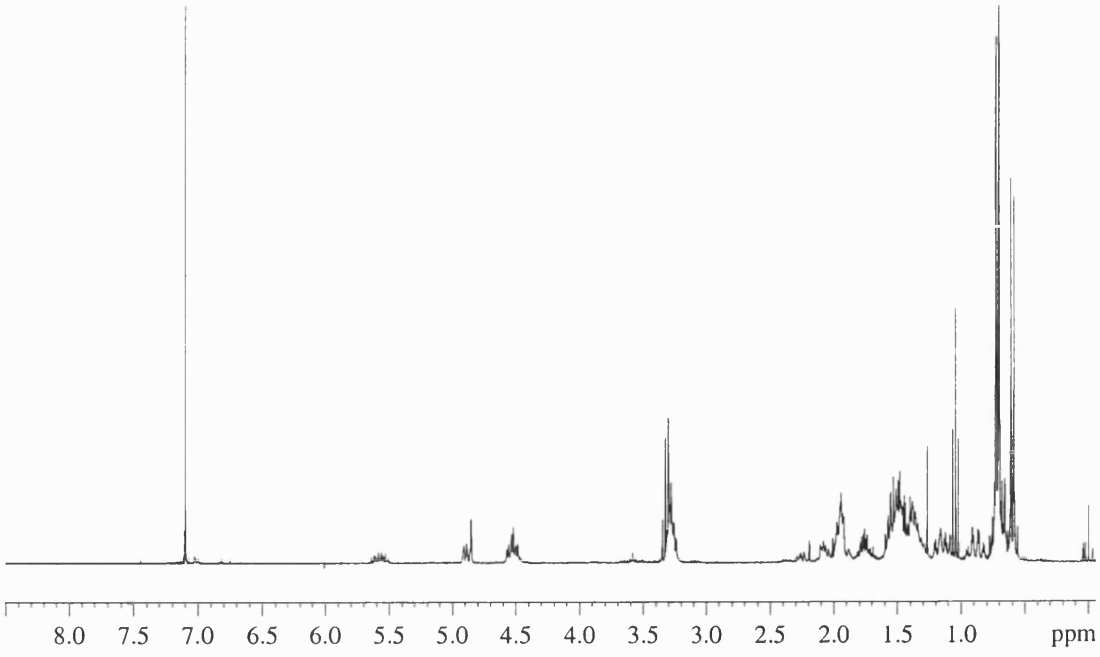
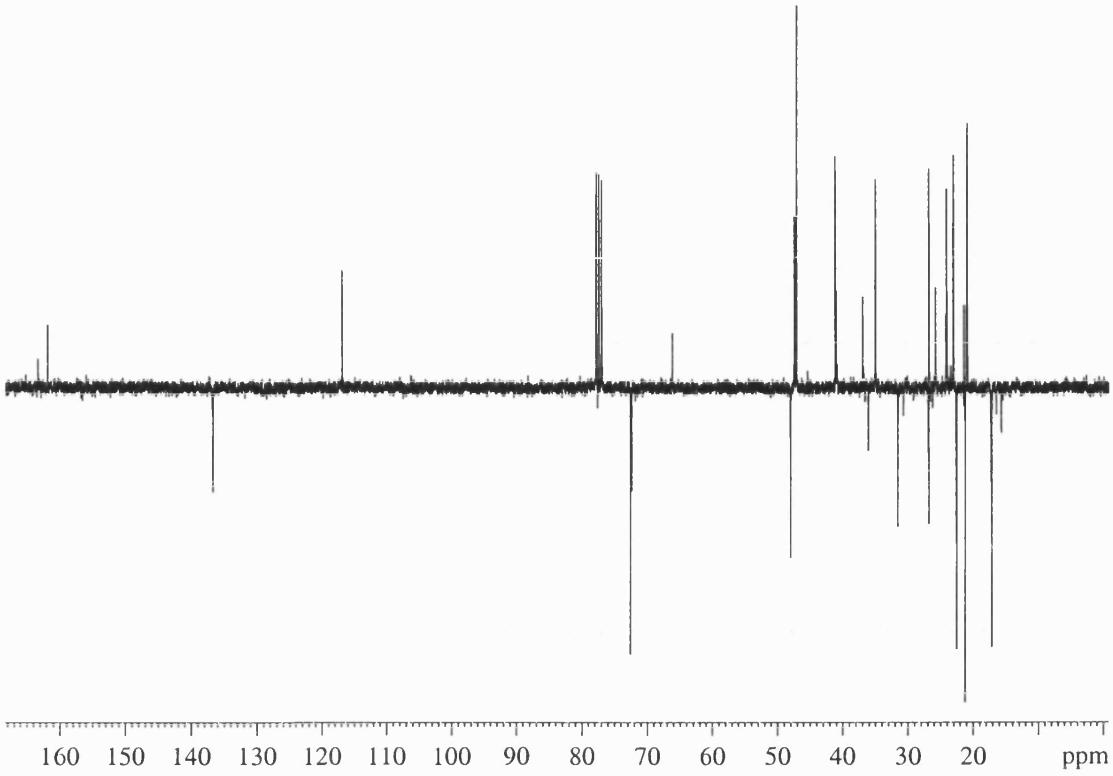



**Figure 3.2.2.** $^{1}$H NMR spectrum of α-allyl (-)-menthol valerolactim ethers **291c/292c**.

This diastereomeric ratio was confirmed by analysis of the $^{13}$C NMR spectrum of the crude reaction product that revealed two sets of resonances in a 4:1 ratio, with peaks

corresponding to virtually all of the resonances expected from a 4:1 ratio of diastereomers. (Figure 3.2.3.)



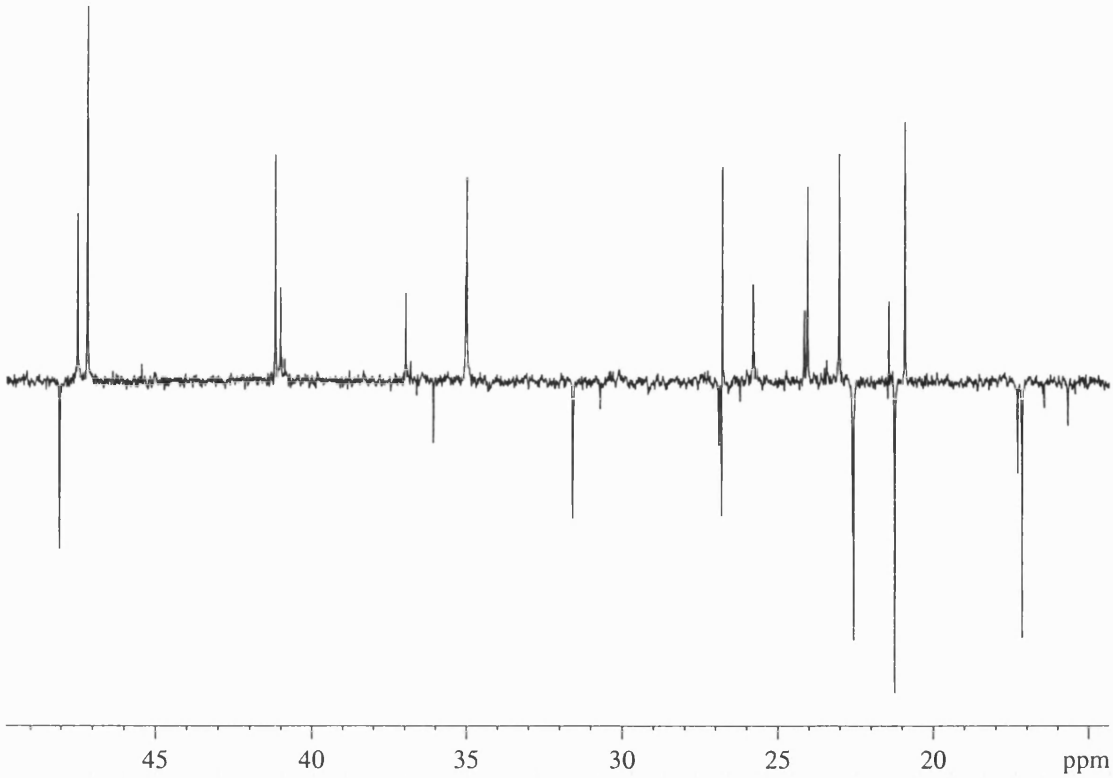



**Figure 3.2.3.** $^{13}C$ NMR spectrum of α-allyl (-)-menthol valerolactim ethers **291c/292c** clearly showing the presence of diastereomeric resonances.

Unfortunately, all attempts to purify either of the major or minor diastereomers of the 4:1 mixture of **291c/292c** to homogeneity *via* exhaustive column chromatography proved unsuccessful. Both diastereomers exhibited identical $R_F$ values on TLC, whilst no evidence of any fractionation of the 4 :1 diastereoisomeric ratio was evident from analysis of early or late chromatographic fractions.

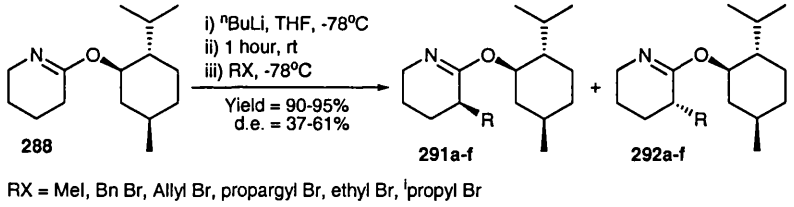
Given the inseparability of the two diastereomers **291c/292c** by chromatographic methods characterisation of their diastereomeric ratio was best achieved by the use of gas chromatographic mass spectroscopy. The results of this analysis revealed the presence of two new compounds with similar retention times and identical fragmentation patterns, expected for the α-allyl (-)-menthol lactim ether diastereomers **291c/292c**. Therefore, fragments corresponding to loss of a methyl group at 262, loss of an $^{i}$propyl at 234, as well as the lactim ether core produced from bond fission either side of the alkyloxy bond at 140 and 122 were observed. Integration of the intensities of the gas chromatography of the baseline resolved peaks of the diastereomers enabled the

diastereomeric excess of this *aza*-enolate alkylation reaction to be confirmed as 45% d.e.

## 3.2.6. Formation of a series of diastereomerically enriched α-alkyl (-)-menthol lactim ethers

The optimised enolate alkylation conditions for chiral lactim ether **288** were then applied to a representative series of electrophiles to afford a range of α-alkyl lactim ethers. Therefore, lactim ether **288** was treated with 2.4 equivalents of $^{n}$BuLi in THF at -78 °C, before warming to room temperature for one hour, recooling to -78 °C, followed by addition of 3 equivalents of the appropriate electrophile. These alkylation reactions proceeded uneventfully, affording quantitative conversion of starting material to α-alkyl product **291a-f/292a-f** as witnessed by $^{1}$H NMR spectroscopic analysis. TLC analysis of each of these crude reaction products revealed a single spot for all of the crude reaction products, whilst exhaustive column chromatography of the methylated lactim ether crude reaction product once again failed to afford any diastereomeric enrichment.

Consequently, each of these (-)-menthol lactim ether *aza*-enolate alkylation reactions were characterised as mixtures of diastereomers using $^{1}$H NMR, $^{13}$C NMR, IR and GCMS analysis, that demonstrated physical and spectroscopic data consistent with the formation of mixtures of *mono*-alkyl (-)-menthol lactim ether diastereomers. GCMS was once again employed as the main diagnostic tool for determining the diastereomeric excesses of these α-alkyl species, with all mixtures of diastereoisomers being base line resolved with each peak affording mass spectrum fragmentation patterns consistent with those expected for this class of compound. This GCMS analysis revealed that a range of α-alkyl lactims **291a-f/292a-f** had been formed in 37-61% d.e. in essentially quantitative yield, with notably higher d.e.'s being recorded for less reactive electrophiles such as ethyl and $^{i}$propyl bromide. (Scheme 3.2.9.)




**Scheme 3.2.9.** Alkylation of the *aza*-enolate of **288** with a range of electrophiles.

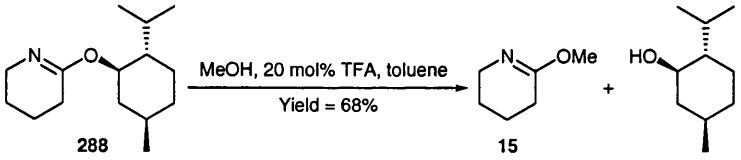
| Entry | Electrophile | $\delta_H$ | % yield | d.e. |
|---|---|---|---|---|
| 1 | MeI | 1.06 (Me) | 92 | 57 |
| 2 | BnBr | 2.43 and 3.05 (2 x $CH_AH_BAr$) | 95 | 37 |
| 3 | AllylBr | 4.90, 4.92 and 5.62 (3 x allyl) | 92 | 45 |
| 4 | EtBr | 0.82 ($CH_3$) | < 90 | 46 |
| 5 | PropargylBr | 1.85 (C≡C-*H*) | 94 | 38 |
| 6 | $^i$PrBr | 0.78, 0.87 ($CH(CH_3)_2$) | < 90 | 61 |

**Table 3.2.1.**

## 3.2.7. Removal of the (-)-menthol chiral auxiliary *via* transesterification

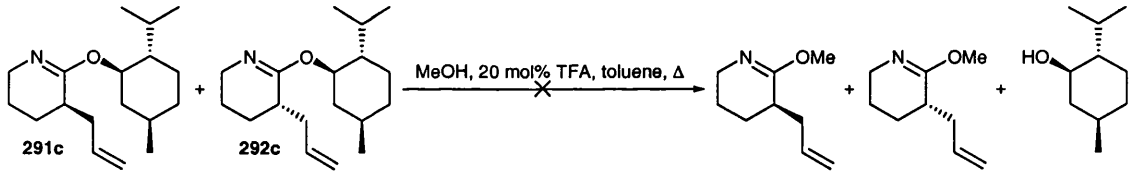
Despite the inability to purify the major α-alkyl diastereomers to homogeneity, my attention then turned to identifying conditions that would enable replacement of the mentholoxy chiral group of chiral lactim ether **288** by methanol, thus affording their corresponding α-alkyl valerolactim ethers.

Given that (-)-menthol lactim ether **288** had been formed from reaction of the parent valerolactim ether **15** with excess (-)-menthol using 1.3 equivalents of TFA as catalyst, it was proposed that these conditions could also be employed to transesterify (-)-menthol lactim ether **288** with methanol. Therefore, (-)-menthol lactim ether **288** was treated with a 30 fold excess of methanol using 1.3 equivalents of TFA in toluene, resulting in clean removal of the (-)-menthol auxiliary after 16 hours to afford valerolactim ether **15** in 68% yield, after Kügelrohr distillation. (Scheme 3.2.10.)




**Scheme 3.2.10.** Removal of the (-)-menthol chiral auxiliary of (-)-menthol valerolactim ether **288** *via* transesterification with methanol.

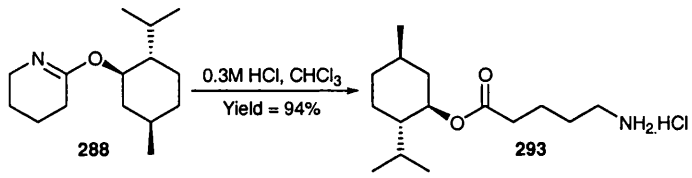
However, application of these conditions to the 4:1 mixture of the two α-allyl (-)-menthol valerolactim ether diastereomers **291c/292c** with 30 equivalents of methanol in the presence of 1.3 equivalents of TFA did not result in transesterification, instead returning recovered starting material in quantitative yield. As a result the reaction was modified by heating to reflux, however once again this reaction did not to produce the desired lactim ether product, once again returning recovered starting material **291c/292c**. Therefore, it appears that the acid catalysed transesterification reaction of lactim ethers appears to be highly sensitive to the presence of α-alkyl substituents, which presumably act to sterically block approach of the incipient nucleophilic alcohol at the imine carbon atom of the lactim ether. (Scheme 3.2.11.)




**Scheme 3.2.11.** Attempted transesterification of **291c/292c**.

## 3.2.8. Preparation of ω-amino α-allyl (-)-menthol ester 293

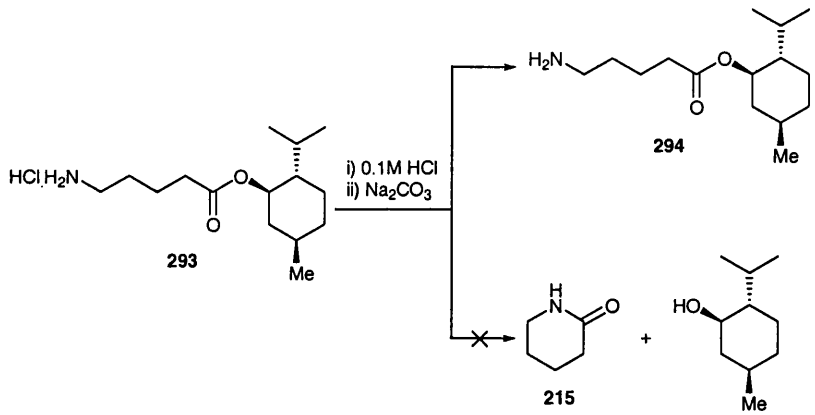
Since conditions could not be identified for the removal of the menthol chiral auxiliary fragment, attention then turned to the development of methodology for direct hydrolysis of the lactim ether bond of (-)-menthol lactim ether **288**. The use of standard hydrolysis conditions using 0.3M HCl, in the presence of a small amount of $CHCl_3$ as cosolvent, resulted in conversion of the parent mentholoxy lactim ether into the desired amino (-)-menthol ester hydrochloride product **293** in essentially quantitative yield. (Scheme 3.2.12.)




**Scheme 3.2.12.** Hydrolysis of **288** to afford ω-amino (-)-menthol amino ester **293**.

Analysis of the $^{1}H$ NMR spectrum of ω-amino ester **293** revealed the diagnostic resonances of the (-)-menthol group unshifted at δ 4.61 (td, *J* 10.9, 4.5 Hz), however the α and δ methylene groups displayed a marked shift from δ 2.05 (m) to δ 2.24 (t, *J* 7.0 Hz) and from δ 3.90 (app. ttt 17.1, 5.7, 1.1 Hz) to δ 2.62 (t, *J* 7.0 Hz). The $^{13}C$ NMR spectrum of **293** revealed the expected 15 resonances with the most diagnostic peak corresponding to the ester carbonyl at 171.1 ppm, which represented a shift of 9 ppm from the previously seen imidic carbon atom of the lactim ether at 162.0 ppm.

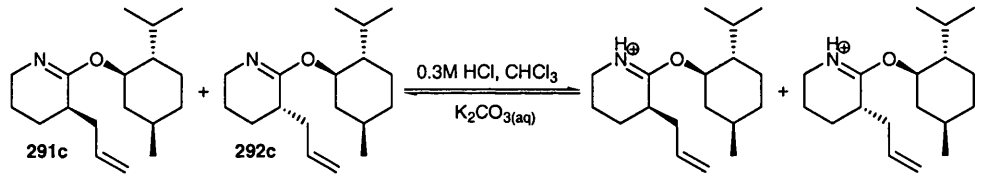
Attempts to promote intramolecular cyclisation of ω-amino (-)-menthol ester **293** *via* neutralisation of the hydrochloride salt *via* treatment with $Na_2CO_{3(aq)}$ to afford (-)-menthol and valerolactam **215** were unsuccessful, instead merely resulting in neutralisation to afford **293** as its free amine **294**. The reason for this failure to cyclise was attributed to the steric bulk of the (-)-menthol group blocking intramolecular attack of the incipient ω-amino nucleophile, at the imine carbon. (Scheme 3.2.13.)




**Scheme 3.2.13.** Unsuccessful cyclisation of the ω-amino ester of (-)-menthol valerolactim ether **293**.

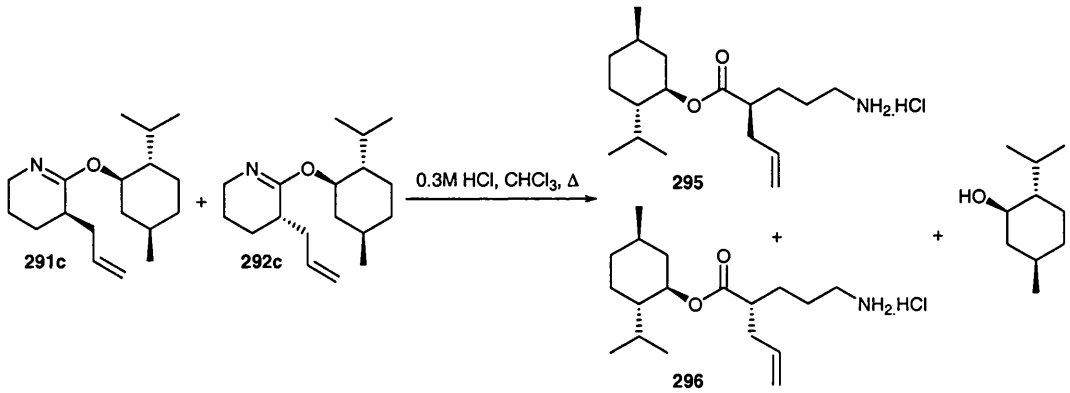
## 3.2.9. Hydrolysis of α-allyl (-)-menthol valerolactim ether

Given the successful hydrolysis conditions (0.3M HCl, $CHCl_3$) established for (-)-menthol valerolactim ether **288** these conditions were then applied to the hydrolysis of the diastereomeric mixture of α-allyl lactim ethers **291c/292c**. Surprisingly, it was found that application of these hydrolysis conditions to α-allyl lactim ether were unsuccessful, returning only quantitative amounts of protonated starting material. This observation was confirmed *via* neutralisation of the protonated material with potassium carbonate solution, which returned a 4:1 mixture of α-allyl (-)-menthol lactim ether diastereomers **291c/292c** once more. (Scheme 3.2.14.)



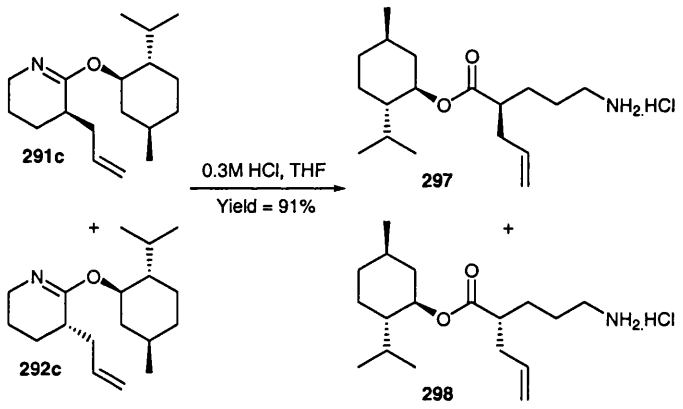

**Scheme 3.2.14.** Attempted hydrolysis of **291c/292c**.

Consequently the reaction was repeated under more forcing condition, involving heating to reflux for 16 hours, the $^1H$ NMR spectrum revealed the formation of a mixture of several compounds that appeared to include the ω-amino esters **295/296** and (-)-menthol. (Scheme 3.2.15.)




**Scheme 3.2.15.** Hydrolysis of **291c/292c** to its esters **295/296**.

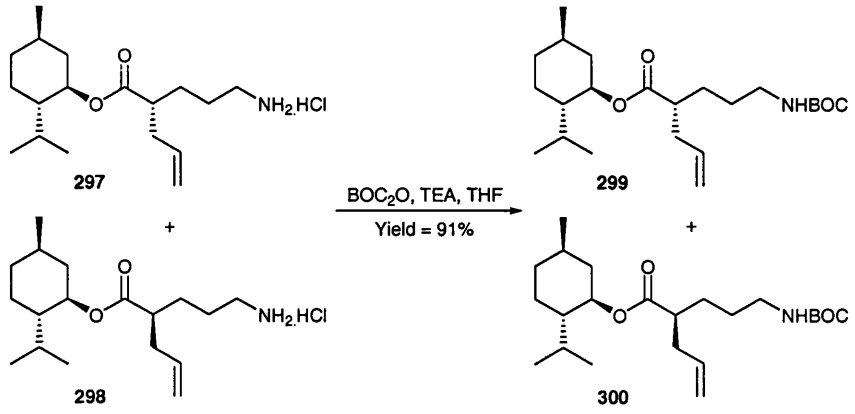
As treatment of **291c/292c** under standard conditions had failed to afford cleanly the desired ω-amino esters **295/296** in good yield, the hydrolysis reaction was repeated using a mixture of THF and 0.3M $HCl_{(aq)}$ solution, reasoning that this mixed solvent system would afford a homogenous solution of the hydrophobic lactim ether. Thus, it was found that dissolving the 4:1 diastereomeric mixture of lactim ether **291c/292c** in 5:1 THF:0.3M HCl solution resulted in clean hydrolysis to afford a 4:1 mixture of α-alkyl ω-amino esters **297/298** in quantitative yield. This observation clearly indicates that hydrolysis under these conditions occurs with no epimerisation of the α-alkyl position of the ester, since the 4:1 ratio of diastereomers was conserved throughout this hydrolysis reaction. (Scheme 3.2.16.)




**Scheme 3.2.16.** Hydrolysis of **291c/292c** to its ω-amino esters **297/298.**

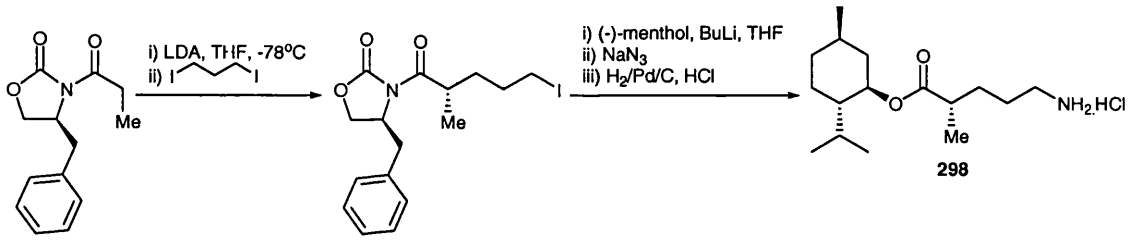
Attempted purification of the 4:1 mixture of diastereomers of the neutralised free amine of **297/298** *via* column chromatography was unsuccessful resulting in no diastereomeric enrichment and a low return of the diastereomers. Therefore, the diastereomeric amines were *N*-protected as their carbamates **299/300** in order to reduce their polarity. Thus, treatment of the 4:1 mixture of diastereomers of amino esters **297/298** in acetonitrile with BOC anhydride in the presence of 2 equivalents of triethylamine afforded a 4:1 diastereomeric mixture of **299/300** in 91% yield. (Scheme 3.2.17.) Unfortunately, numerous attempts to purify the carbamate protected amine **299/300** *via* exhaustive column chromatography once again proved unsuccessful in affording diastereomerically pure samples. This inability to separate this mixture of diastereomers was particularly frustrating, since it meant that three attempts to separate the 4:1 mixtures of α-allyl (-)-menthol lactim ethers **291c/292c**, ω-amino ester **297/298**, and *N*-

BOC ω-amino esters **299/300** had all failed, with all pairs of diastereomers exhibiting identical $R_F$ values. Therefore, it was decide to try and attempt to identify a better chiral auxiliary fragment that would afford improved diastereocontrol in the *aza*-enolate alkylation reaction, as well as affording diastereomers that could be separated by chromatography.




**Scheme 3.2.17.** BOC protection of α-allyl amino (-)-menthol esters **297/298**.

Finally, it should be noted that the configuration of the major diastereomers **291a-f/292a-f** in these *aza*-enolate alkylation reactions currently remains undetermined. This is a result of the fact that the major and minor diastereomers could not be separated, whilst their $^1$H NMR spectra were very similar with many overlapping peaks that prevented NOE studies from being carried out. Preparation of an authentic sample of an α-alkyl ω-amino acid **298** using Evans' enolate alkylation methodology was considered, since its comparison as an authentic standard would enable the configuration of the major diastereomer **306** to be determined. However, given time constraints, and the fact that only moderate diastereocontrol had been observed in *aza*-enolate alkylation reactions, and the inability to purify the major diastereomers to homogeneity, it was decided to concentrate on identifying a more stereoselective chiral auxiliary for asymmetric synthesis. (Scheme 3.2.18.)

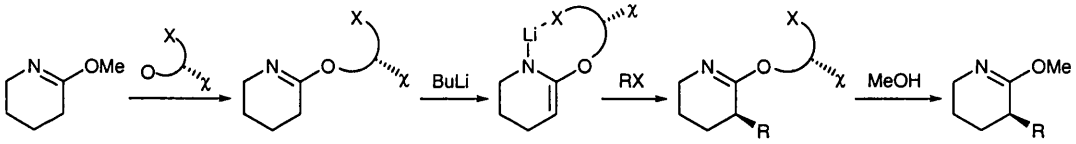



**Scheme 3.2.18.** Formation of an authentic sample of (*S*)-α-methyl α-amino pentanoic acid **298** *via* an Evans' enolate alkylation strategy.

# 3.3. Attempts to develop alternative asymmetric *aza*-enolate alkylation methodology

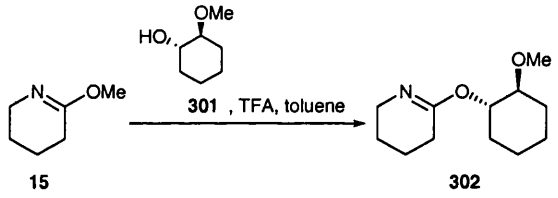
## 3.3.1. Preparation of enantiopure α-alkyl lactim ether derived from a chelating chiral auxiliary

The use of (-)-menthol as a chiral auxiliary for the α-alkylation of the *aza*-enolate of valerolactim ether **288** had occurred in only moderate d.e.'s whilst purification of the resultant mixture of diastereomers had proven unsuccessful. It was proposed that the reason that (-)-menthol had produced moderate d.e.'s was due to the fact that the terpene fragment of the *aza*-enolate could enjoy free rotation around its carbon-oxygen bond, which would result in insufficient energy differences between attack of the electrophile at the *re*- or *si*- faces of the *aza*-enolate. As a consequence an alternative chiral auxiliary fragment was chosen for transesterification that was capable of intramolecular chelation to the lithium counterion of the *aza*-enolate of the lactim ether. This might afford a more rigid transition state similar to that described previously by Bergbreiter *et al.* for their imino ether chiral auxiliary system,[120] which should give higher levels of diastereocontrol than was observed for the (-)-menthol analogue. (Scheme 3.3.1.)




**Scheme 3.3.1.** Proposed approach for the use of intramolecularly chelating chiral auxiliary.

Commercially available (1*S*,2*S*)-2-methoxycyclohexanol **301** was selected as a chiral auxiliary for this task since it offered the possibility of affording a rigid chair conformer, as well as providing an exogenous methoxy group capable of acting as a chelating group to the lithium counterion of a derived *aza*-enolate. Transesterification of valerolactim ether **15** was effected in the usual manner *via* treatment with alcohol **301** in the presence of 1.3 equivalents of TFA, which after purification through Kügelrohr distillation afforded lactim ether **302** in 53% yield. (Scheme 3.3.2.)

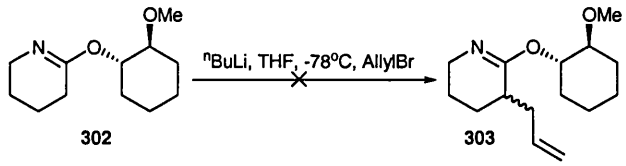



**Scheme 3.3.2.** Transesterification of valerolactim ether **15** with (1*S*,2*S*)-2-methoxycyclohexanol **301**.

Analysis of the $^{1}$H NMR spectrum of lactim ether **302** revealed new resonances corresponding to the $C_1$ and $C_2$ protons of the cyclohexyloxy fragment at δ 4.71 (ddd, *J* 9.6, 8.5 and 4.9 Hz) and δ 3.11 (ddd, *J* 9.6, 8.5, 4.1 Hz), with a new methoxy resonance at δ 3.34 (s). The $^{13}$C NMR spectrum revealed the predicted 12 resonances, whilst the infra red and mass spectrum returned the expected 1681 cm$^{-1}$ and 212.1642.

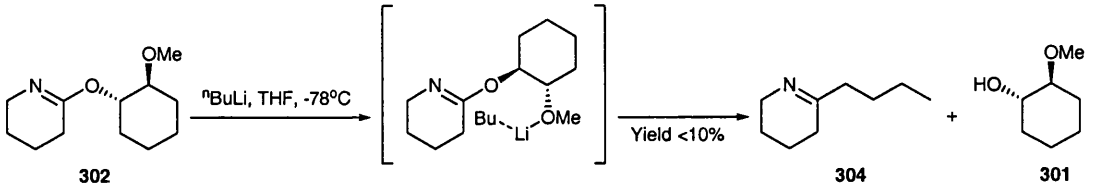
## 3.3.2. Attempted preparation of α-allyl (1*S*,2*S*)-2-methoxycyclohexyloxy lactim ether 303

Attempts to form the *aza*-enolate of (1*S*,2*S*)-2-methoxycyclohexyloxy lactim ether **302** were carried out using a the full range of conditions previously developed for the (-)-menthol derived valerolactim ether **288**. Therefore, addition of 1.3 equivalents of $^{n}$BuLi and warming to room temperature for 1 hour before recooling to -78 °C with subsequent addition of allyl bromide, resulted in recovered starting material **302**, as a well as a trace amount of (1*S*,2*S*)-2-methoxycyclohexanol **301**. (Scheme 3.3.3.) Repetition of the reaction using excess base (3 equivalents); $^{n}$BuLi, LDA or Schlosser's base, did not afford the desired α-alkyl lactim ether **303**, returning good yields of **302**, with small amounts of (1*S*,2*S*)-2-methoxycyclohexanol **301**.




**Scheme 3.3.3.** Attempted alkylation of chiral lactim ether **302**.

Close examination of the $^{1}$H NMR spectra of all three reactions revealed that there was evidence of a small amount of new product containing a triplet at δ 0.91 (t, *J* 7.0 Hz) and methylene groups at δ 1.27 (2H, t, *J* 7.0 Hz) and 1.44-1.59 (4H, m). Therefore, it was proposed that these reactions had not afforded an *aza*-enolate intermediate due to the occurrence of an alternative reaction pathway involving coordination of the lithium counterion of the $^{n}$BuLi to the oxygen atom of the methoxy unit of the chiral auxiliary fragment, followed by delivery of butyl anion as a nucleophile to the imine carbon atom of **302**. However, this reaction represented a minor pathway as the yield from the $^{1}$H NMR spectra of the crude reaction product was <10% in each case. (Scheme 3.3.4)

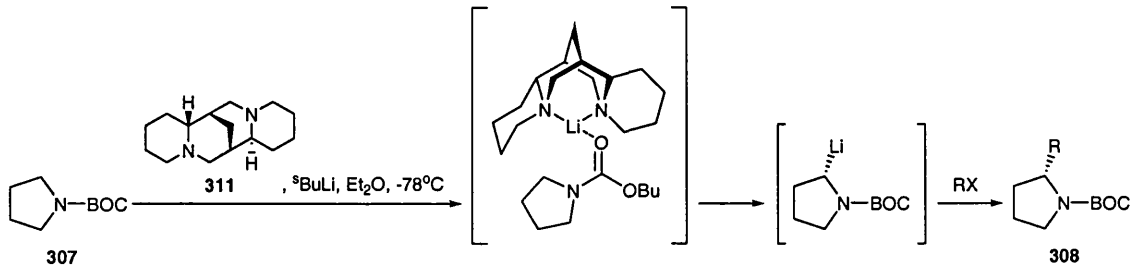



**Scheme 3.3.4.** Reaction of lactim ether **302** with to afford the BuLi to afford an $^{n}$butyl imine **304** and (1*S*,2*S*)-2-methoxycyclohexanol **301**.

# 3.4. Asymmetric alkylation of lactim ethers using a chiral ligand approach

## 3.4.1. Alkylation of the *aza*-enolate of lactim ethers in the presence of (-)-sparteine as a chiral ligand

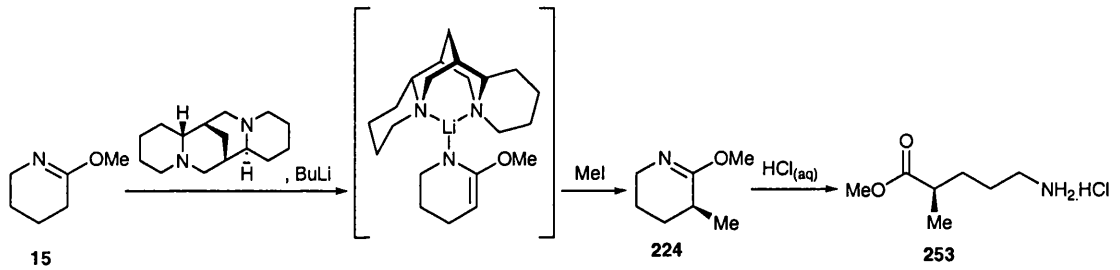
Concurrent to the chiral auxiliary studies described above, I attempted to develop a chiral ligand strategy to carry out symmetric *aza*-enolate alkylation reactions. The use of chiral ligands in stereoselective organic reactions is well documented with many chiral ligand systems have been reported in the literature, however (-)-sparteine **306** remains the most notable example. (-)-Sparteine **306** was first reported as a chiral ligand in 1968, however, it was not regularly employed for asymmetric synthesis until Hoppe *et al.* reported its use in asymmetric lithiation and substitution reactions in 1990. It has subsequently been employed for a wide range of asymmetric transformation, including for the alkylation of *N*-BOC pyrrolidine **307** *via* enantioselective lithiation using a $^{s}$BuLi/(-)-sparteine combination, that afforded α-alkyl pyrrolidinones **308** in high e.e.[141] (Scheme 3.4.1.)




**Scheme 3.4.1.** Asymmetric alkylation of *N*-BOC pyrrolidinone **307** *via* a (-)-sparteine **306** mediated approach.

## 3.4.2. Asymmetric synthesis of α-methyl valerolactim ether 224 using (-)-sparteine 306 as a chiral ligand

My attempts to synthesise α-alkyl lactim ether **224** in enantiopure form followed a variation of the precedents Beak and of O'Brien,[141-143] employing two equivalents of (-)-sparteine **306** which was mixed with two equivalents of $^{n}$BuLi in THF at -78 °C for 15 minutes, before lactim ether **15** was added as a pre-cooled solution in THF. The resultant solution was then allowed to warm to room temperature and stirred for one hour in an attempt to form a (-)-sparteine *aza*-enolate complex, before being recooled to -78 °C, and methyl iodide added dropwise before the reaction mixture was allowed to stir overnight. (Scheme 3.4.2.)



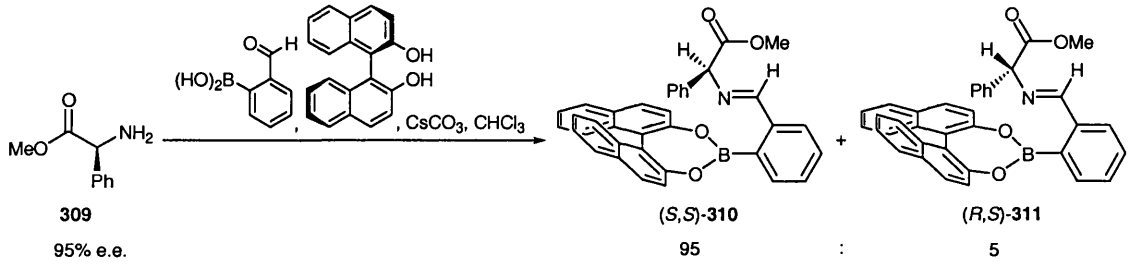

**Scheme 3.4.2.** Proposed approach for the production of chiral α-methyl lactim ethers **224** using (-)-sparteine.

Analysis of the crude $^{1}$H NMR and $^{13}$C NMR spectra of **303** was difficult due to the presence of excess (-)-sparteine **306** in the crude reaction product, however it was

determined that the *aza*-enolate reaction had proceeded in high conversion from the presence of a new methoxy resonance at δ 3.53 (s), $CH_2N$ resonances δ 3.39 (tt, *J* 5.8 and 1.2 Hz), as well as a distinctive methyl doublet δ 1.09 (d, *J* 7.0 Hz), that was partially obscured by the upfield resonances of (-)-sparteine **306**. Purification of α-methyl lactim ether **224** by exhaustive column chromatography was attempted, however all attempts were unsuccessful due to (-)-sparteine **306** co-eluting with the methylated product **224**. However, Kügelrohr distillation did prove successful in affording a pure sample of α-methyl lactim ether **224** in good yield (73%).

Analysis for any signs of enantiomeric excess for this sample of α-methyl lactim ether **224** was initially carried out *via* determination of its specific rotation. Disappointingly, the specific rotation measured for α-methyl lactim ether **224** was essentially zero. This suggested that α-methyl lactim ether **224** had been formed in essentially racemic form with the (-)-sparteine chiral ligand **306** acting as a simple spectator in the reaction. In order to confirm this conclusion, α-methyl lactim ether **224** was hydrolysed to its α-methyl ω-amino ester **315** whose enantiomeric excess was then determined using a new chiral derivitising protocol recently developed in the Bull group.

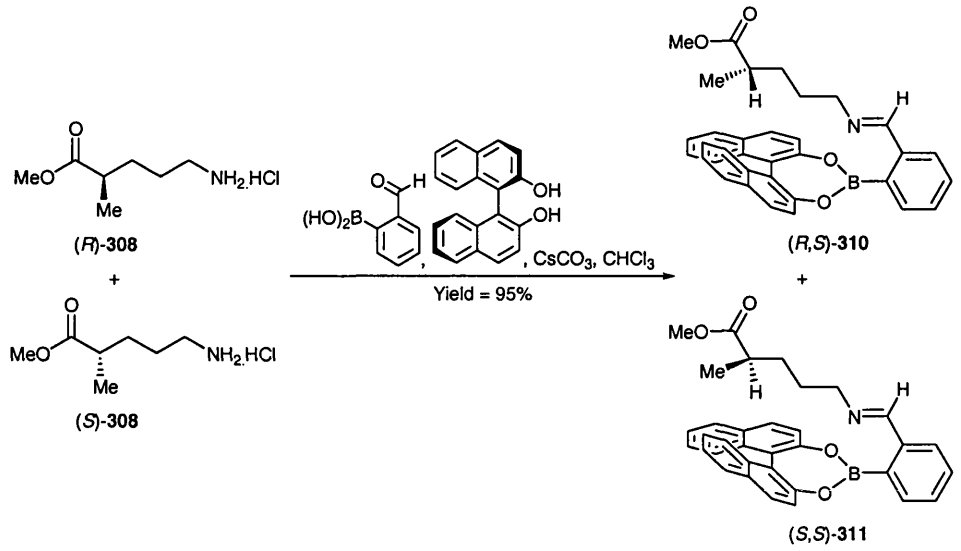
This approach involves treatment of a primary amine with enantiopure BINOL and 2-formyl boronic acid, which results in a three component coupling reaction to afford a mixture of diasteromeric BINOL-imine-boronate complexes. For the case of racemic amines and enantiopure BINOL the two diastereomeric complexes that are formed have been shown to display well resolved $^1$H NMR and $^{13}$C NMR spectra for a wide range of substrates, whose resonances may be integrated to determine the enantiomeric excess of a sample of amine. For example, treatment of α-phenylglycine methyl ester **309** of 90% e.e. with this chiral derivitisation agent, was shown to afford a 95:5 mixture of amine-BINOL-boronate complexes (*S*,*S*)-**310**/(*S*,*R*)-**311** *via* $^1$H NMR spectroscopic analysis (see Appendix B). (Scheme 3.4.3.)




**Scheme 3.4.3.** Formation of (*S*)-BINOL-imine-boronate complex from phenyl glycine.

Furthermore, it has been shown that this chiral derivitising agent is capable of discriminating between stereocentres that are remote from the point of attachment of the amine, thus making it potentially ideal for determining the enantiomeric excess of α-methyl ω-amino ester **253**.

The (-)-sparteine mediated sample of α-methyl ω-amino ester hydrochloride salt **253** was treated with caesium carbonate in $CDCl_3$ in the presence of one equivalent of 2-formyl boronic acid and one equivalent of (*S*)-BINOL for five minutes in the presence of 4Å molecular sieves. Subsequent 400MHz $^1$H NMR spectroscopic analysis revealed that a clean three component self-assembly reaction had occurred to afford a 50:50 mixture of two diastereomeric boronate-BINOL-imine complexes (*S*,*S*)-**310**/(*S*,*R*)-**311**. This 50:50 ratio of diastereomers was determined from analysis of the equal intensities of the two methyl doublet resonances of each diastereomer at δ 0.85 and δ 0.87 which were baseline resolved. Importantly, the 50:50 mixture of diastereomers in the $^1$H NMR spectrum of the (-)-sparteine derived α-methyl ω-amino ester-boronate-(*S*)-BINOL derivitisation reaction was identical to the $^1$H NMR spectrum of the (*S*)-BINOL-boronate complex of an authentic racemic sample of α-methyl ω-amino ether **253** prepared previously.




**Scheme 3.4.3.** Self-assembly diastereomeric complexes derived from α-methyl ω-amino ester **253**, 2-formyl phenyl boronic acid and (*S*)-BINOL.

Clearly, the potential for racemisation of the stereocentre of the α-methyl valerolactim ether **224** during the derivitisation process must be considered. Firstly, it was shown previously that no epimerisation of the 4:1 mixture of α-allyl menthol valerolactim ether diastereoisomers **291c/292c** occurred during hydrolysis to their corresponding α-alkyl ω-amino esters **297/298** under mildly acidic conditions. Secondly, derivitisation of a wide range of other primary amines with this chiral derivitising agent has been shown to occur without racemisation occurring.[144] For example, easily racemisable enantiopure α-arylglycine methyl ester **309** has been shown to afford single diastereomeric BINOL-imine-boronate complexes when treated with this chiral derivitising agent under these conditions. Therefore, these spectroscopic analyses, coupled with the lack of specific rotation for α-methyl lactim ether, indicate that α-methyl valerolactim ether **224** was formed in racemic form during the (-)-sparteine mediated *aza*-enolate alkylation reaction.

Finally, the ability of this chiral derivitising agent to discriminate the α-methyl stereocentre of ω-amino ester **253** that is four bonds from the point of attachment of the amine to the imine is particularly noteworthy, and contrasts with commonly employed Mosher's amide derivatives that generate only discriminate between diastereoisomers with α-stereocentres. This ability is likely to be due to the formation of rigid

diasteromeric complexes, in which the aryl units of the BINOL fragment exert different anisotropic shielding effects on each diastereomer.

## 3.5. Conclusion

The principle of employing a chiral auxiliary to control facial selectivity for the diastereoselective alkylation of the *aza*-enolate of valerolactim ether has been demonstrated. (-)-Menthol has been used as a chiral auxiliary fragment for this purpose, with effective strategies having been developed for introducing and removing the chiral auxiliary *via* an acid catalysed transesterification approach. The diastereoselectivity observed in the alkylation of the *aza*-enolate of a (-)-menthol derived lactim ether was moderate, ranging from 38-61% d.e., whilst the major and minor diastereomers could not be separated by chromatography. This inability to purify the major diastereomer to homogeneity ultimately renders this approach ineffective for the preparation of enantiopure α-alkyl ω-amino esters (or α-alkyl lactams).

Attempts to employ (1*S*,2*S*)-methoxycyclohexanol as a chiral auxiliary was unsuccessful due to the occurrence of a competing nucleophilic addition pathway, whilst the use of (-)-sparteine as an exogenous chiral ligand proved ineffective, affording racemic products in good yield.

Clearly, the asymmetric *aza*-enolate alkylation methodology described in this section needs further development, however I believe that the original principle has been demonstrated and offers a good precedent for developing alternative chiral auxiliary based system that offers improved stereocontrol. Current work ongoing in the Bull group is directed towards screening a range of chiral alcohols as chiral auxiliaries, in an attempt to identify highly stereoselective chiral lactim ether substrates.

# Chapter 4

# Results and Discussion

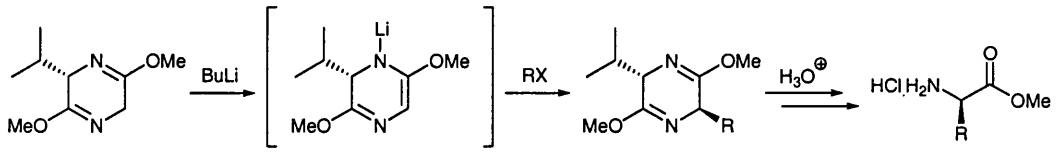
# Isotopic labelling of *bis*-lactim ether chiral auxiliaries for the production of isotopically labelled phenylalanines

# Chapter 4. Extension of Schöllkopf's *bis*-lactim ether methodology

## 4.1. Schöllkopf's *bis*-lactim ether methodology

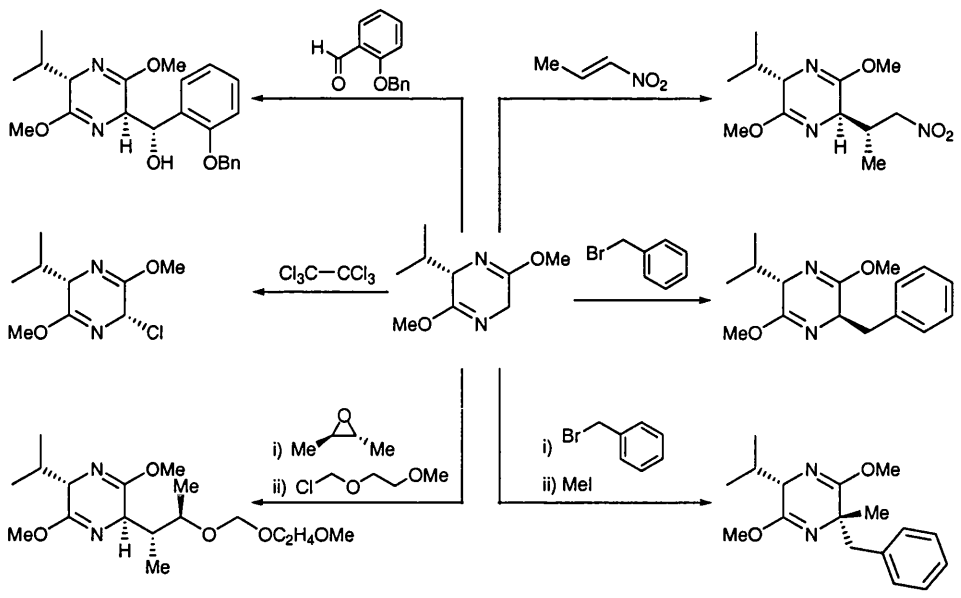
### 4.1.1. Formation of enantiopure amino esters using *bis*-lactim ether methodology

Schöllkopf's *bis*-lactim ether methodology represents one of the most commonly used protocols for the synthesis of enantiopure α-amino esters owing to its highly stereoselective *aza*-enolate alkylation step,[119, 126] and the mild conditions employed for lactim ether bond hydrolysis. This *aza*-enolate methodology has been applied to many electrophilic sources, thus affording a multitude of different types of α-substituted α-amino ester products. Initial work by Schöllkopf *et al.* showed that the *aza*-enolate of *bis*-lactim ethers could be *trans*-alkylated with electrophiles to afford *trans*-alkylated lactim ethers, that could be purified to homogeneity and hydrolysed to their component α-amino esters in excellent yield,[117, 118, 126] (Scheme 4.1.1.)




**Scheme 4.1.1.** Formation and alkylation of the *aza*-enolate of *bis*-lactim ether **203**.

Since this first report on *aza*-enolate alkylations, effective protocols have been developed that employ *bis*-lactim ether **203** for asymmetric aldol,[145] conjugate addition,[146] halogenation[147] and *bis*-alkylation[117, 118, 148] reactions. (Scheme 4.1.2.)



**Scheme 4.1.2.** Alkylation of *bis*-lactim ether **203**.

The success of this chiral auxiliary for asymmetric synthesis is clear from the wide range of α-amino esters that have been reported to date, with over 2000 examples of its use having been detailed to date. (Figure 4.1.1.)

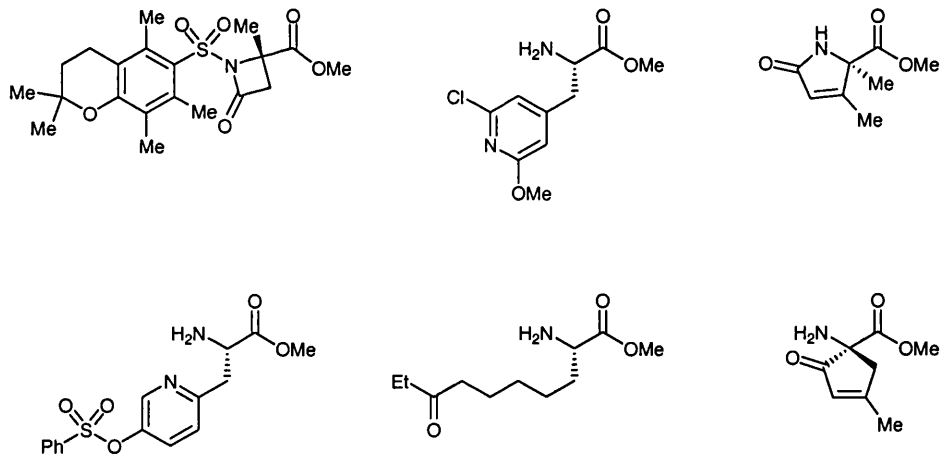


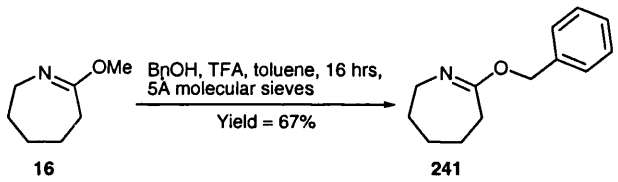
**Figure 4.1.1.** Structures of six α-amino esters recently synthesised *via* Schöllkopf's methodology.[149-154]

# 4.2. Potential improvements of Schöllkopf's *bis*-lactim ether chiral auxiliary methodology

It was proposed that two important discoveries relating to the chemistry of lactim ethers described in chapter 2 might have important applications for the chemistry of Schöllkopf's *bis*-lactim ether methodology.

## 4.2.1. Transesterification precedent for lactim ethers

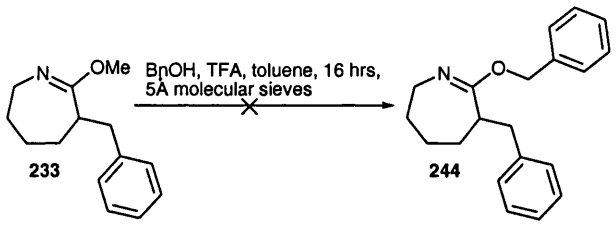
Firstly it has been shown in section 2.3.4. that lactim ethers readily undergo transesterification reaction with alcohols in the presence of acid to afford lactim ether products containing a new alkyloxy fragment. For example, this approach was employed using capro **16** and oenantholactim methyl ether **237** substrates to afford their corresponding benzyl lactim ethers **241** and **242** in good yield. (Scheme 4.2.1.)




16 241

**Scheme 4.2.1.** Transesterification of caprolactim ether **16** with benzyl alcohol.

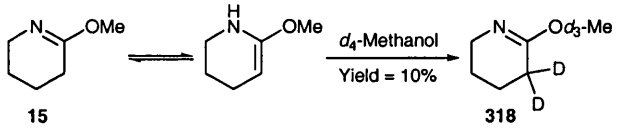
Further work in this area has shown that the presence of an α-alkyl substituent within the lactim ether substrate retarded this transesterification reaction dramatically. For example, in the case of α-benzyl caprolactim ether **233** it was found that no transesterification reaction occurred upon treatment with benzyl alcohol in the presence of 1.3 equivalents of TFA, with an essentially quantitative yield of α-benzyl methyl caprolactim ether **233** being recovered. (Scheme 4.2.2.)




**Scheme 4.2.2.** Unsuccessful attempted transesterification of α-benzyl caprolactim ether **233** with benzyl alcohol.

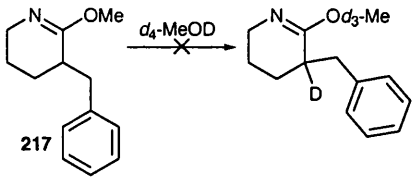
## 4.2.2. Isotopic labelling precedent for lactim ethers

Secondly it was found that when valerolactim ether **15** was left in $d_4$-methanol for several weeks that an isotopically labelled $d_3$-methoxy fragment was incorporated into the alkyloxy position of the lactim ether **318**. However, it was also noted that the integration of the resonance at δ 3.41 (dt, *J* 5.7 and 1.2 Hz) corresponding to the two methylene protons at the α-position also decreased in intensity over a similar timescale. This was attributed to slow tautomerisation of the lactim ether occurring in the presence of a readily available deuterium source resulting in slow incorporation of deuterium at its α-centre.




**Scheme 4.2.3.** Isotopic labelling of the alkyloxy and α-position of valerolactim ether **15**.

Furthermore, it was also noted that the presence of an α-alkyl group within the lactim ether substrate retarded this deuteration reaction, since treatment of α-benzyl valerolactim ether **217** with $d_4$-methanol failed to afford α-deuterated α-benzyl valerolactim ether **319** even after being left for several months. (Scheme 4.2.4.)

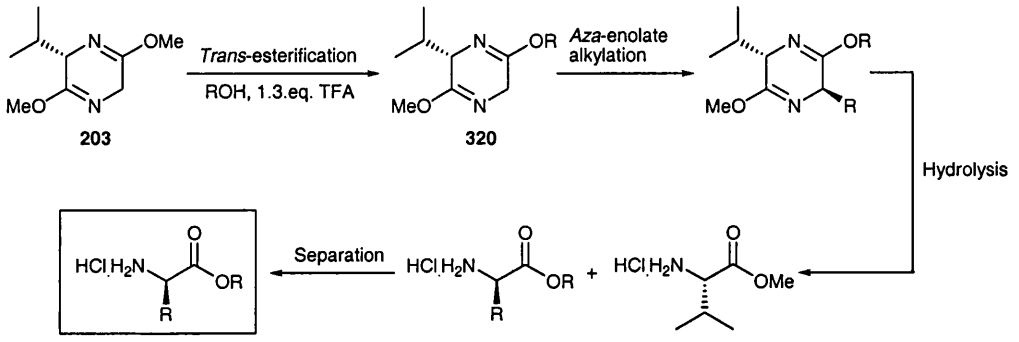



**Scheme 4.2.4.** Unsuccessful isotopic labelling of α-benzyl valerolactim ether **217**.

It was recognised that these observations had potentially useful applications for the use of Schöllkopf's *bis*-lactim ether methodology, and now described is the investigation into this area.

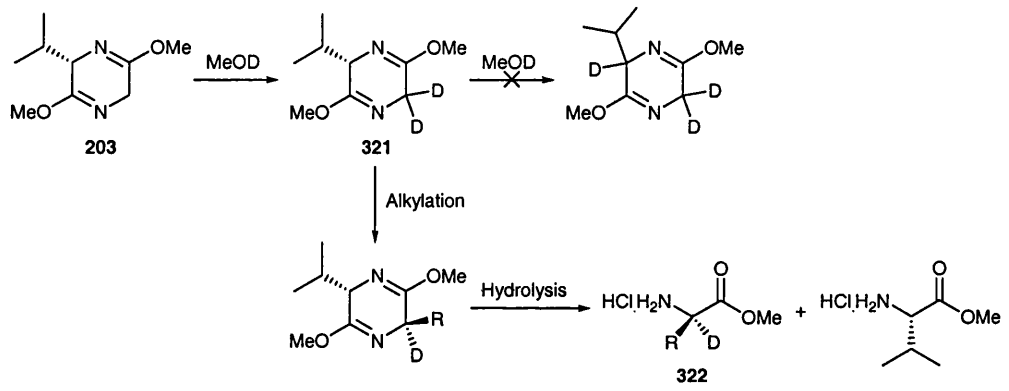
## 4.2.3. Potential applications of transesterification and isotopic labelling reactions on Schöllkopf's *bis*-lactim ether methodology

It was proposed that both the transesterification and isotopic labelling reactions described above could have potential applications if applied to Schöllkopf's *bis*-lactim ether chiral auxiliary. For example, regioselective transesterification reaction of *bis*-lactim ether **203** would result in a *bis*-lactim ether **320** containing chemically inequivalent alkyloxy groups. *Aza*-enolate alkylation of **320** followed by acidic hydrolysis would afford α-amino esters with differing ester groups that could improve separation of the chiral auxiliary L-valine methyl ester fragment from the desired α-alkyl α-amino ester. (Scheme 4.2.5.)




**Scheme 4.2.5.** Transesterification strategy for affording orthogonally protected *bis*-lactim ethers **320**.

Alternatively, deuteration of *bis*-lactim ether **203** with $d_1$-methanol might potentially afford selective access to a *bis*-lactim ether chiral auxiliary **321** isotopically labelled with deuterium at its $C_6$, which in turn would afford enantiopure isotopically labelled α-alkyl α-amino esters **322**. As described previously, the presence of an α-alkyl group hinders the enamine tautomerisation process of lactim ethers, which should prevent incorporation of deuterium at the $C_3$ $^i$propyl stereocentre of the *bis*-lactim ether **203**, which would be catastrophic because it would serve to racemise the chiral auxiliary. (Scheme 4.2.6.)



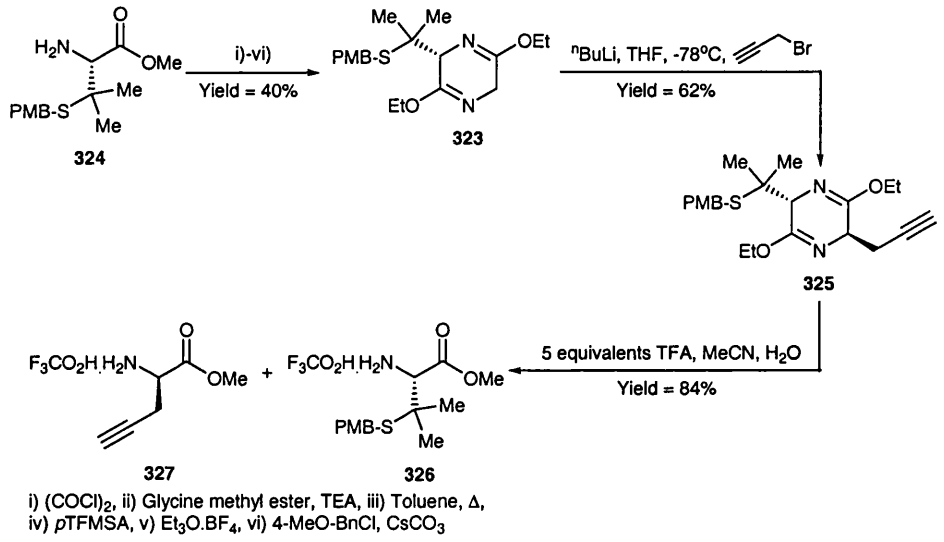

**Scheme 4.2.6.** Deuteration of *bis*-lactim ether **203** at its $C_6$ without racemisation of the $C_3$ stereocentre.

# 4.3. Synthesis and use of orthogonally protected *bis*-lactim ether

## 4.3.1. Practical problems associated with the use of Schöllkopf's chiral auxiliary

As described, Schöllkopf's chiral auxiliary is one of the most widely employed synthetic routes to enantiopure α-amino esters, however, despite its popularity there remains a major problem associated with its use. This occurs on hydrolysis of the *trans*-alkylated *bis*-lactim ether substrate to its component α-amino esters, which must be separated *via* either chromatography or distillation. This separation is often far from ideal, particularly if the target molecule is a low molecular weight α-amino ester that is

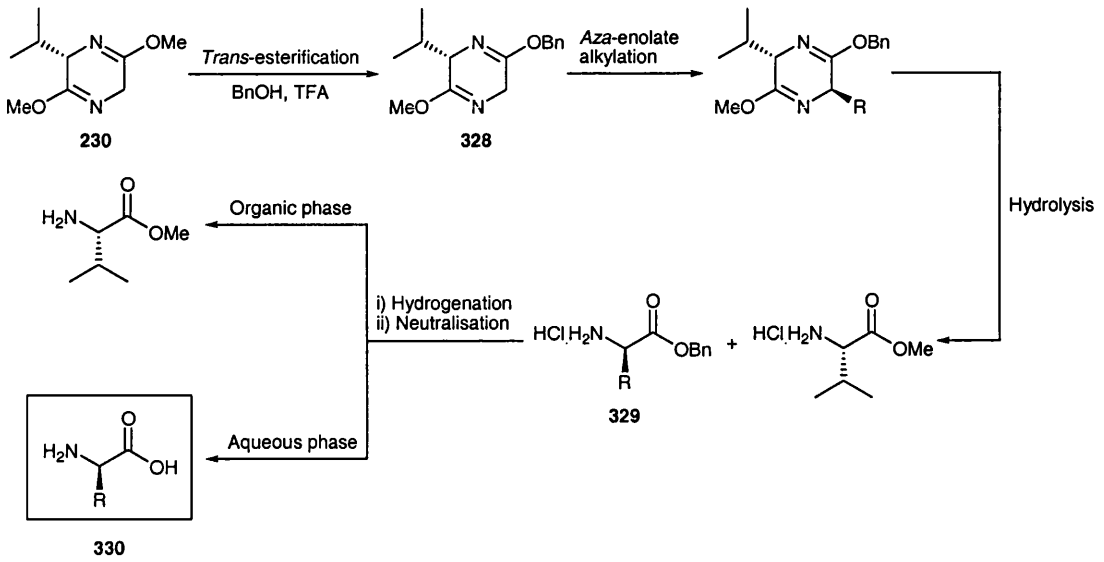
required on a significant scale. Recognising this problem, Richter *et al.* developed an *S*-protected penicillamine derived *bis*-lactim ether **323** for asymmetric synthesis, which they synthesised in a moderate 40% overall yield from *S*-PMB penicillamine **324**.[155] They reported that the alkylation of its *aza*-enolate with propargyl bromide proceeded in reduced 64% yield to afford the *trans*-propargylated *bis*-lactim ether **325**. Subsequent cleavage of *trans*-propargylated *bis*-lactim ether **325** in aqueous acetonitrile in the presence of five equivalents of TFA afforded a mixture of the *S*-PMB penicillamine derived chiral auxiliary ethyl ester **326**, and the desired α-amino ethyl ester **327** as their TFA salts in 84% yield. This mixture of α-amino esters was then separated by simple partition between $CH_2Cl_2$ and water, since *S*-PMB penicillamine ethyl ester TFA salt was soluble in $CH_2Cl_2$, whilst the newly formed α-amino ester remained in the aqueous phase. (Scheme 4.3.1.)




**Scheme 4.3.1.** Formation of (*S*)-α-propargyl α-amino ethyl ester **327** using penicillamine *bis*-lactim ether **323**.

However, penicillamine **326** is an expensive non-proteinogenic amino acid that ultimately limits the use of this methodology for the asymmetric synthesis, and as a consequence it was proposed that this separation problem might also be resolved if the orthogonally protected *bis*-lactim ether **328** was used for synthesis. It was proposed that treatment of Schöllkopf's *bis*-lactim ether chiral auxiliary **203** with benzyl alcohol in the presence of TFA might result in a selective transesterification to afford an *O*-methyl

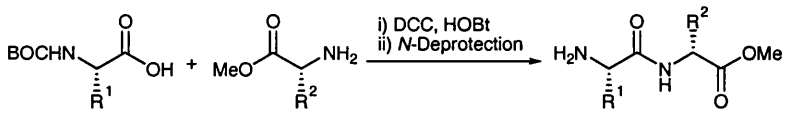
*O*-benzyl *bis*-lactim ether **328**. It was suggested that once this chiral auxiliary was *trans*-alkylated and hydrolysed, then facile purification of the resultant mixture of L-valine methyl ester and the desired enantiopure α-amino benzyl ester **329** could then be achieved by simple hydrogenolysis. This hydrogenolytic step would therefore result in a mixture of the desired α-amino acid **330** and L-valine methyl ester which could be easily separated *via* partition between water and an organic solvent. (Scheme 4.3.2.)




**Scheme 4.3.2.** Overview of the proposed methodology for the use of *O*-methyl *O*-benzyl *bis*-lactim ether **328**.

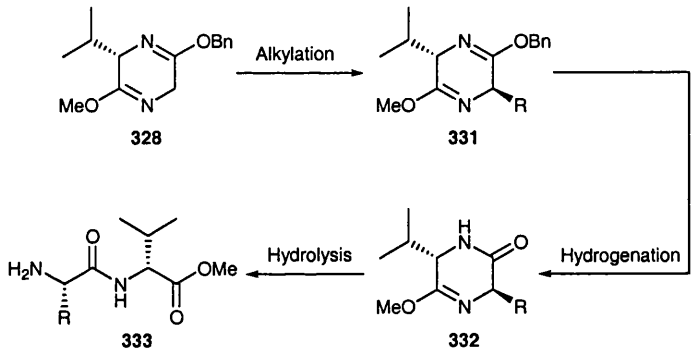
## 4.3.2. Synthesis of dipeptide species using orthogonally protected *bis*-lactim ether

Dipeptides represent a core functionality that are common in many natural and medicinally active products, and as such represent valuable synthetic targets.[156, 157] Current methodology for the production of this class of compound usually employ amide bond coupling reactions between α-amino esters through judicious choice of nitrogen and ester protecting groups as well as coupling reagents such as DCC and HOBt. (Scheme 4.3.3.)




**Scheme 4.3.3.** DCC coupling of *N*-BOC valine and phenylalanine methyl ester.

It was proposed that the presence of the two different alkyloxy units of *bis*-lactim ether **328** might also enable an orthogonal deprotection strategy to afford dipeptide products. For example, alkylation of the *aza*-enolate of Schöllkopf's chiral auxiliary **328** would afford its *trans*-alkylated *O*-methyl *O*-benzyl *bis*-lactim ether **331** which on hydrogenation would afford a masked cyclic dipeptide derivative **332**, containing both amide and lactim ether bonds. Taking into account the differing reactivities of these two functionalities, mild acidic hydrolysis should result in selective cleavage of the lactim ether bond to selectively afford the desired dipeptide **333**. (Scheme 4.3.4.)

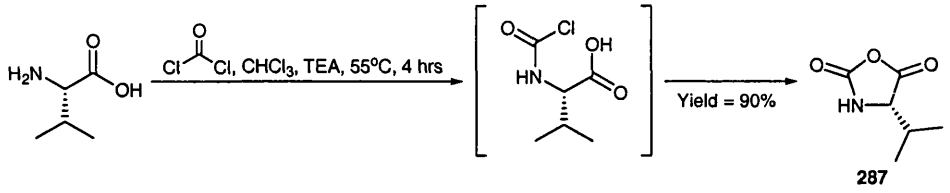



**Scheme 4.3.4.** Overview of the synthesis of dipeptides from *O*-methyl *O*-benzyl *bis*-lactim ether **328**.

Whilst the example described is for an L-valine derived *bis*-lactim ether **328**, this protocol is potentially applicable to other *bis*-lactim ethers available from other α-amino esters, thus potentially affording access to a wide range of proteinogenic and non-proteinogenic dipeptides.

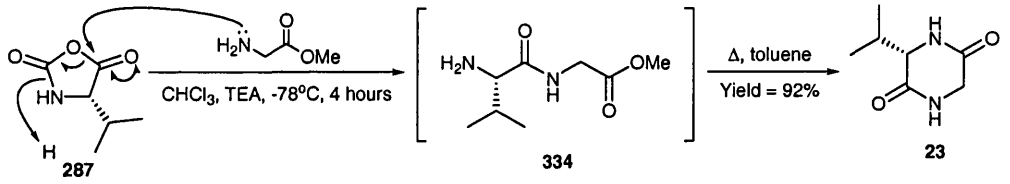
## 4.3.3. Preparation of *bis*-lactim ether 328

*Bis*-lactim ether was prepared *via* a four stage literature synthesis starting from L-valine.[130] The initial step involved formation of the Leuch's anhydride of L-valine *via* treatment with 20% phosgene solution in toluene to afford Leuch's anhydride **287** in 90% yield. (Scheme 4.3.5.)



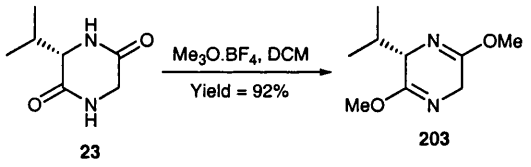

**Scheme 4.3.5.** Formation of the Leuch's anhydride of L-valine **287**.

Leuch's anhydrides readily undergo nucleophilic ring opening reactions with concomitant loss of carbon dioxide, thus treatment with an α-amino ester results in dipeptide formation. Therefore, reaction of Leuch's anhydride **287** with glycine methyl ester afforded an unstable intermediary dipeptide methyl ester **334** which was cyclised without isolation *via* heating to reflux in toluene to afford (*S*)-3-isopropylpiperazine-2,5-dione **23** in 92% yield over two steps. (Scheme 4.3.6.)




**Scheme 4.3.6.** Ring opening of Leuch's anhydride **287** with glycine methyl ester to afford diketopiperazine **23**.

Thus treatment of diketopiperazine **23** with three equivalents of trimethyloxonium tetrafluoroboronate **221** afforded *bis*-lactim ether **203** in 72% yield after careful neutralisation of the resultant *bis*-tetrafluoroboronate salt under basic conditions. (Scheme 4.3.7.)

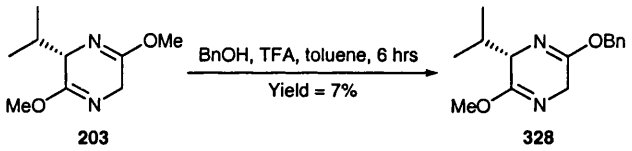



23 203

**Scheme 4.3.7.** Formation of *bis*-lactim ether **203** from the corresponding diketopiperazine **23** *via* the use of Meerwein's salt.

## 4.3.4. Production of *O*-methyl *O*-benzyl *bis*-lactim ether 328

With multigram quantities of *bis*-lactim ether **203** in hand, attention turned towards developing an efficient transesterification protocol for the synthesis of *O*-methyl *O*-benzyl *bis*-lactim ether **328**. Thus, treatment of *bis*-lactim ether **203** with one equivalent of benzyl alcohol in the presence of 1 equivalent of TFA and 5Å molecular sieves for 6 hours succeeded in the formation of *bis*-lactim ether **328** in a low 7% yield after column purification. (Scheme 4.3.8.)



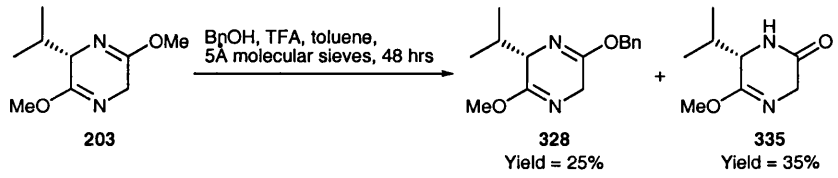

203 328

**Scheme 4.3.8.** Transesterification of *bis*-lactim ether **203** with benzyl alcohol under acidic conditions to afford a 7% yield of *O*-methyl *O*-benzyl *bis*-lactim ether **328**.

Analysis of the $^{1}H$ NMR spectrum of *bis*-lactim ether **328** revealed the presence of two resonances relating to the $^{i}$propyl group at δ 0.63 (d, *J* 7.0 Hz) and δ 0.94 (d, *J* 7.0 Hz), further to this the presence of two resonances relating to the benzylic methylene protons were noted δ 4.98 (d, *J* 12.2 Hz) and δ 5.18 (d, *J* 12.2 Hz). The presence of a benzyl group was further confirmed by the presence of an aromatic resonance between δ 7.18-7.34 (bm). The $^{13}C$ NMR spectrum revealed the expected thirteen resonances, whilst a mass of 261.1598 was present in its mass spectrum.

Analysis of the $^{1}H$ NMR spectrum of the crude reaction mixture revealed that the remainder of the reaction mixture was comprised of unreacted starting *bis*-lactim ether

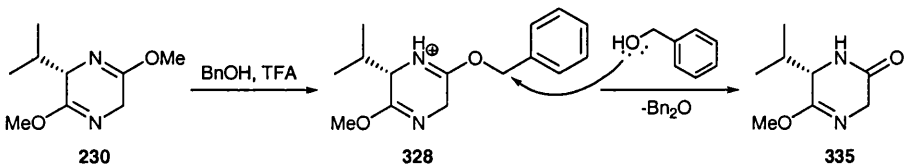
**203** and benzyl alcohol, and as a consequence a series of optimisation reactions were carried out. These studies revealed that treatment of *bis*-lactim ether **203** with 1 equivalent of benzyl alcohol in the presence of 1 equivalent of TFA and 5Å molecular sieves for two days afforded an increased 25% yield of *O*-methyl *O*-benzyl *bis*-lactim ether **328**. However, it was noted from analysis of the $^1$H NMR spectrum and TLC of the crude reaction product that a polar by-product had been formed in approximately 35% yield, which was eventually isolated through column chromatography. This by-product was shown to be the *mono*-lactim ether species **335**, which was proposed to have been formed through protonation of the *bis*-lactim ether **203** and subsequent *O*-dealkylation *via* attack of a molecule of benzyl alcohol, as previously observed during hydrolysis of α,α-di$^i$butyl valerolactim ether **230** in section 2.2.10. (Scheme 4.3.9.)




**203** **328** Yield = 25% **335** Yield = 35%

**Scheme 4.3.9.** Dealkylation of *bis*-lactim ether **328** by benzyl alcohol under acidic conditions.

As very little *mono*-lactim ether **335** had been formed in the initial reaction of *bis*-lactim ether **203** with benzyl alcohol over six hours, coupled with the fact that the lability of the *O*-benzyl bond had proven problematic for benzyl caprolactim ether **241**, it was proposed *mono*-lactim ether **335** was formed primarily from nucleophilic attack of the benzyl alcohol upon *O*-methyl *O*-benzyl *bis*-lactim ether **328**, and not from the parent *bis*-lactim ether **203**. (Scheme 4.3.10.)

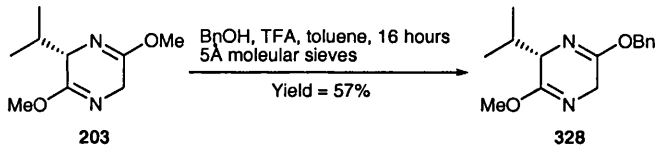



**230** **328** **335**

**Scheme 4.3.10.** Nucleophilic attack of benzyl alcohol on protonated *O*-methyl *O*-benzyl *bis*-lactim ether **328** to afford *mono*-lactim ether **335**.

Optimisation of the reaction time revealed that 16 hours provided the best compromise between the formation of unwanted *mono*-methyl lactim ether **335** and unreacted *bis*-lactim ether **203**, affording *bis*-lactim ether **328** in 37% isolated yield.

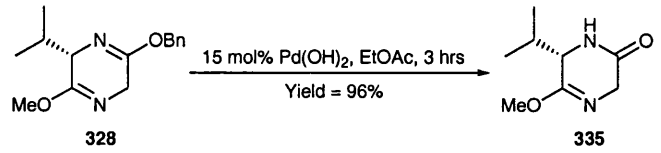
Finally, it was noted that molecular sieves are mildly basic[158] and as a consequence the number of molecular sieves was limited to avoid unnecessary sequestration of the TFA acid source. Thus, it was found that treatment of *bis*-lactim ether **203** in toluene with 1.5 equivalents of benzyl alcohol in the presence of 1.3 equivalents of TFA and one equivalent of 5Å molecular sieves resulted in the formation of *O*-methyl *O*-benzyl *bis*-lactim ether **328** in 57% isolated yield. (Scheme 4.3.11.)




**Scheme 4.3.11.** Transesterification of *bis*-lactim ether **203** with benzyl alcohol to afford *O*-methyl *O*-benzyl *bis*-lactim ether **328**.

## 4.3.5. Confirmation of the structure of *O*-methyl *O*-benzyl *bis*-lactim ether 328

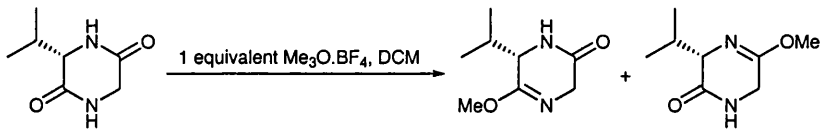
In order to confirm the structure of *O*-methyl *O*-benzyl *bis*-lactim ether **328** it was proposed that facile hydrogenation would allow easy access to the previously reported *mono*-methyl lactim ether **335**,[130] which I had also isolated as a by-product of the transesterification reaction. Therefore, treatment of *bis*-lactim ether **328** with 15 mol% Pearlman's catalyst in EtOAc under an atmosphere of hydrogen afforded *mono*-methyl lactim ether **335** in 96% yield. (Scheme 4.3.12.)




328 335

**Scheme 4.3.12.** Hydrogenation of *O*-methyl *O*-benzyl *bis*-lactim ether **328** to afford *mono*-methyl lactim ether **335**.

However the $^{1}H$ NMR and $^{13}C$ NMR spectra obtained for the hydrogenation of *bis*-lactim ether **328** were different from the spectra previously reported by Bull *et al.* for this compound raising doubts over the assigned structure. Closer examination of the previous report by Bull *et al.* revealed that **335** had been formed as a 2:1 mixture of the *mono*-methyl lactim ether regioisomers **335** and **336** formed by treatment of diketopiperazine **23** with one equivalent of trimethyloxonium tetrafluoroboronate. Furthermore, the structures of these two regioisomers had been assigned by virtue of relatively small nOe effects that could possibly have been open to misinterpretation. Indeed, examination of the $^{1}H$ NMR spectroscopic data assigned by Bull *et al.* to *mono*-lactim ether **336** revealed it to be essentially identical to the data I had assigned to the structure of *mono*-lactim ether **335**. (Scheme 4.3.13.)




23 335 336

**Scheme 4.3.13.** Bull *et al.* *O*-alkylation of diketopiperazine **23** to afford the *mono*-methyl lactim ether **335** and **336**.

Fortunately, *mono*-methyl lactim ether **335** was a crystalline solid and suitable crystals could be isolated for X-ray crystal analysis which revealed the expected structure which could only have been derived from the expected *O*-methyl *O*-benzyl *bis*-lactim ether **328**. Therefore, the crystal structure clearly revealed the presence of the methoxy group distal to the $^{i}$propyl group, with a proximal amidic carbonyl group. The ring system adopted a half-boat conformation, with the $^{i}$propyl group occupying a pseudo axial orientation shielding one face of the ring. (Figure 4.3.1)

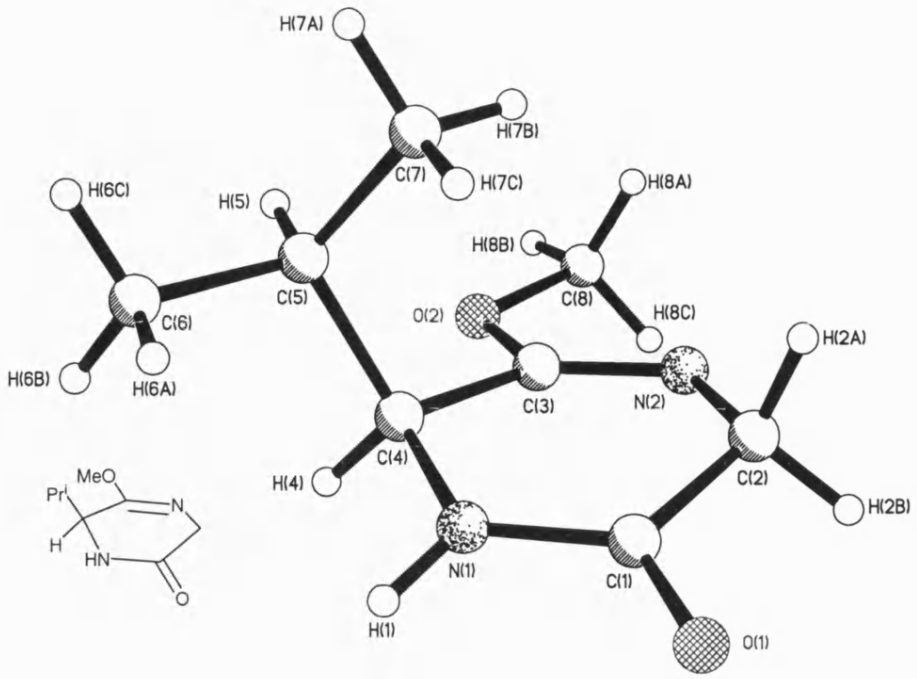



**Figure 4.3.1.** X-ray crystal structure of *mono*-lactim ether **335**.

Analysis of the X-ray crystal superstructure of *mono*-lactim ether **335** revealed that if had formed an oligomeric ladder structure through hydrogen bonding between the N-H and the carbonyl groups of alternate amide bonds of adjacent *mono*-lactim ether monomers. (Figure 4.3.2.)

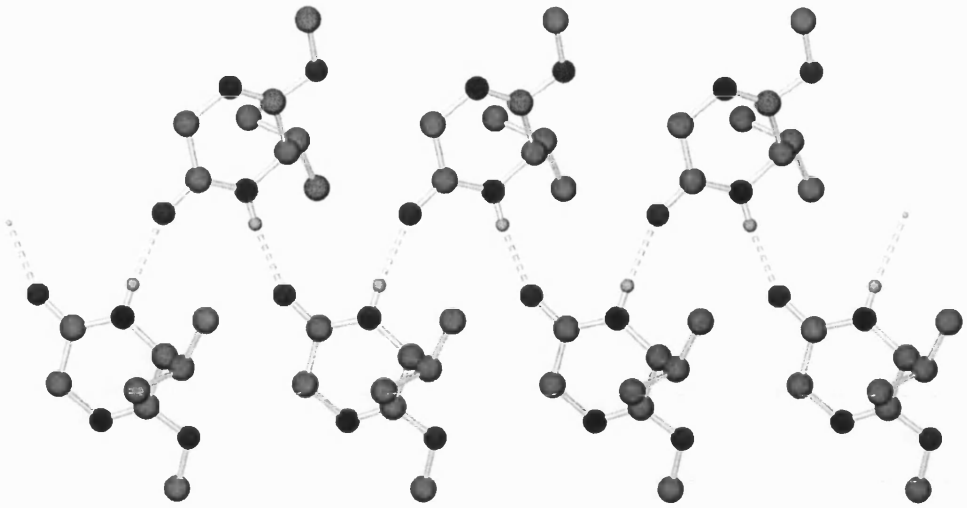


**Figure 4.3.2.** Crystal structure of mono-lactim ether **335** demonstrating the oligomeric ladder structure it forms.

The hydrogen bond lengths observed were; N-H bond 0.885Å; H-O 1.978Å (2.859Å overall), whilst the dihedral angle was 173.36°, which represents typical hydrogen bond lengths and angles for this type of extended ladder network derived from amidic bonds.[159] (Figure 4.3.3.)

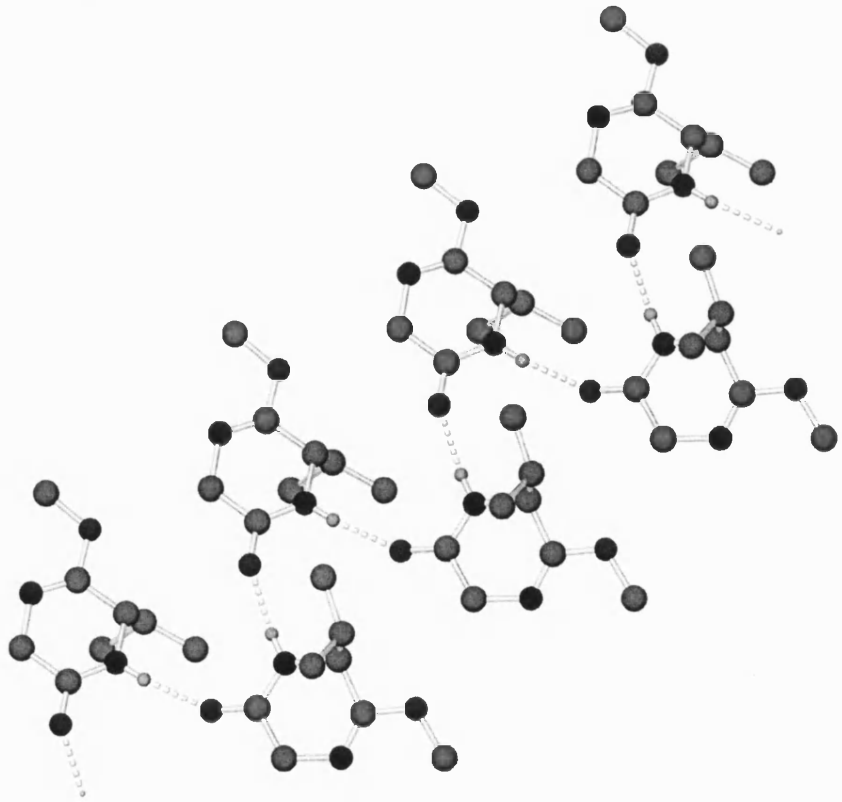
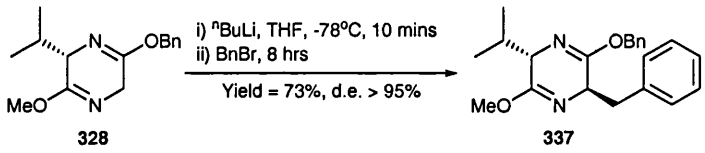


**Figure 4.3.3.** Crystal structure of mono-lactim ether **335**.

Clearly, these crystallographic findings mean that spectroscopic assignments for the *mono*-methyl lactim ether regioisomers **335** and **336** originally reported by Bull *et al.* are incorrect and that the structures of the two isomers assigned to the spectroscopic data in this original report should be reversed.

## 4.3.5. Alkylation of the *aza*-enolate of *O*-methyl *O*-benzyl *bis*-lactim ether 328

Attempts to alkylate the *aza*-enolate of *O*-methyl *O*-benzyl *bis*-lactim ether **328** proceeded well according to documented literature precedent,[119, 126, 132, 160] since treatment with $^{n}$BuLi in THF at -78 °C for 10 minutes under an atmosphere of nitrogen, followed by addition of benzyl bromide, gave *trans*-benzylated *O*-methyl *O*-benzyl *bis*-lactim ether **337** in high yield and >90% d.e. The crude product was readily purified to homogeneity *via* column chromatography to afford *trans*-benzylated *bis*-lactim ether **337** in 73% yield and >95% d.e. (Scheme 4.3.14.)



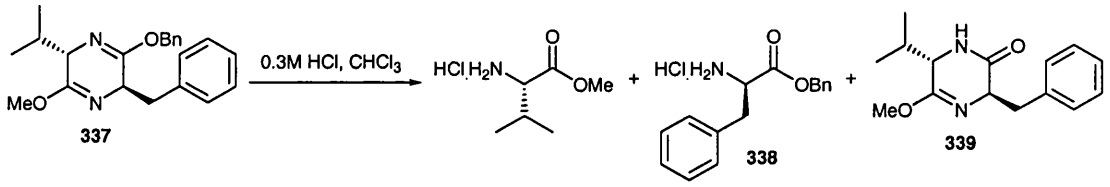

328 337

**Scheme 4.3.14.** Benzylation of the *aza*-enolate of *bis*-lactim ether **328** to afford *trans*-benzylated *O*-methyl *O*-benzyl *bis*-lactim ether **337**.

Analysis of the $^{1}$H NMR spectrum of **337** revealed the presence of two resonances relating to the $^{i}$propyl group, δ 0.47 (d, *J* 7.0 Hz) and δ 0.86 (d, *J* 7.0 Hz), a resonance relating to the newly added benzylic methylene group δ 3.02 (d, *J* 8.3 and 3.4 Hz) and δ 3.07 (app t, *J* 3.4 Hz) and a resonance relating to the alkyloxy benzylic methylene protons δ 5.03 (d, *J* 7.7 Hz) and δ 5.11 (d, *J* 7.7 Hz). The $^{13}$C NMR spectrum revealed the expected eighteen resonances, whilst a mass of 351 was recorded in its mass spectrum.

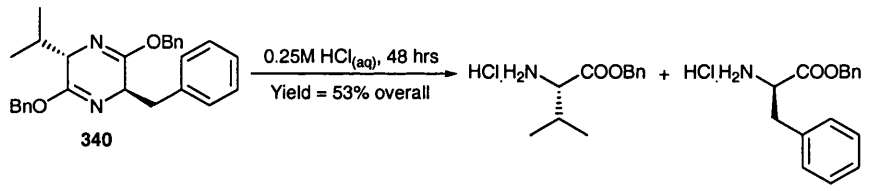
## 4.3.6. Attempted hydrolysis of *trans*-benzylated *O*-methyl *O*-benzyl *bis*-lactim ether 337

Hydrolysis of a small amount (10 mg) of *trans*-benzylated *O*-methyl *O*-benzyl *bis*-lactim ether **337** was attempted using conditions previously developed for the *mono*-alkyl valerolactim ethers. However, treatment with the mixed solvent system of $CHCl_3$/0.3M HCl did not result in clean hydrolysis affording a complex mixture of products. Analysis of the $^1H$ NMR spectra of the crude reaction product implied competing formation of *trans*-benzylated *mono*-methyl lactim ether amide **339** which had presumably been formed due to the lability of the *O*-benzyl bond under acidic conditions. This was evidenced by the presence of resonances corresponding to valine methyl ester and the phenylalanine benzyl ester **338** hydrochloride salts in the $^1H$ NMR spectrum, as well as new peaks at δ 5.61 (bs), δ 3.81 (s), δ 0.86 (d, *J* 7.0 Hz), and δ 0.91 (d, *J* 7.0 Hz) assigned to the NH, OMe, and $^i$propyl groups of *trans*-benzylated *mono*-lactim ether **339**. Unfortunately attempts to purify this reaction mixture to homogeneity *via* column chromatography proved unsuccessful due to the small amount (<6 mg) of material available. (Scheme 4.3.15.)




**Scheme 4.3.15.** Attempted hydrolysis of *trans*-benzylated *bis*-lactim ether **337**.

Interestingly Schöllkopf *et al.* have reported previously that hydrolysis of benzyl *bis*-lactim ether **340** had proceeded in only 53% yield, implying that a significant loss of material that might also have occurred *via* this type of debenzylation pathway. (Scheme 4.3.16.)

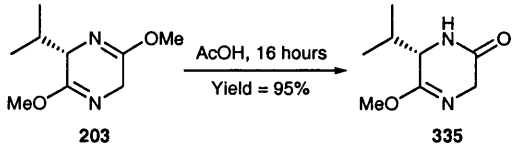



**Scheme 4.3.16.** Schöllkopf's hydrolysis of *trans*-benzylated *bis*-benzyl lactim ether **340**.

Unfortunately, due to a shortage of *bis*-lactim ether substrate **203** I was unable to repeat the hydrolysis reaction of **337** under these conditions, and this work will now be investigated further by another member of the Bull group.

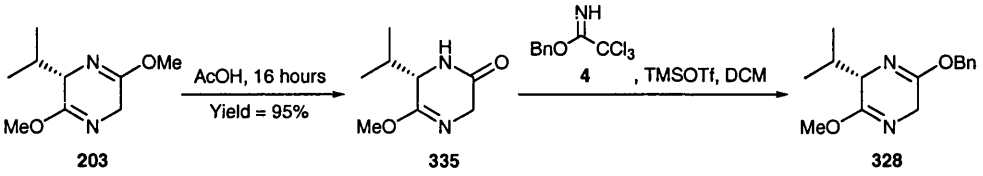
## 4.3.7. Regioselective demethylation of *bis*-lactim ether 203

The work described above represents a potentially exciting extension to the methodology of Schöllkopf, however even if the hydrolysis reaction can be optimised, then the 57% yield recorded for formation of the parent lactim ether **328** is clearly unsatisfactory. It was proposed that access to *O*-methyl *O*-benzyl *bis*-lactim ether **328** might be achieved *via* a step-wise synthesis of *mono*-methyl lactim ether **335**. It was proposed that *bis*-lactim ether **203** had the potential to undergo regioselective *O*-demethylation to afford **335** in the presence of strong acid and an appropriate nucleophilic source. As a result, a series of acids were screened for their ability to regioselectively demethylate *bis*-lactim ether **203** to afford a reliable and robust route to *mono*-lactim ether **335**. Thus, it was eventually found that treatment of *bis*-lactim ether **203** with glacial acetic acid for sixteen hours selectively afforded *mono*-methyl lactim ether **335** in essentially quantitative yield. (Scheme 4.3.17.)




**Scheme 4.3.17.** Regioselective demethylation of *bis*-lactim ether **203** using acetic acid.

It had already been shown by Schöllkopf *et al.* that diketopiperazine **23** could be readily converted into *bis*-benzyl lactim ether **340**, *via* treatment of **23** with benzyl trichloroacetimidate in the presence of TMSOTf as a Lewis acid. Therefore, treatment of mono-lactim ether **335** with benzyl trichloroacetimidate and TMSOTf under these conditions should afford a facile route to *O*-methyl *O*-benzyl *bis*-lactim ether **328**. (Scheme 4.3.18.)




**203** **335** **328**

**Scheme 4.3.18.** Proposed formation of *O*-methyl *O*-benzyl *bis*-lactim ether **328**, using benzyl trichloroacetimidate **4** and TMSOTf.

## 4.4. Isotopic labelling of lactim ethers and preparation of enantiopure α-deuterated α-amino acids

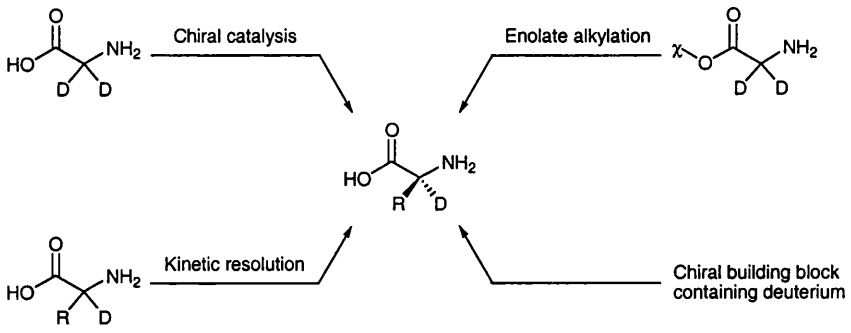
Concurrent to my studies into the use of orthogonally protected *bis*-lactim ether **328**, I also sought to identify a viable synthetic route to $d_2$-labelled *bis*-lactim ether **321** with the aim of employing it for the asymmetric synthesis of a series of isotopically labelled α-amino esters.

### 4.4.1. Current uses of isotopically labelled amino acids

α-Deuterated α-amino acids represent a valuable synthetic tool in many scientific disciplines due to their ability to afford compounds that can be interrogated *via* NMR spectroscopy. For example, this ability enables this class of compound to be employed as probes for elucidation of biosynthetic pathways,[161-164] as well as tools for investigation of the secondary and tertiary structures of peptides and proteins.[165-168]

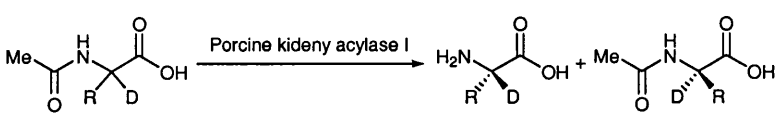
## 4.4.2. Current synthetic methods for the production of enantiopure α-deuterated α-amino acids

As a result of their desirability there exist many routes to the synthesis of isotopically labelled enantiopure α-amino acids. Many of the routes share a common scheme involving introduction of the isotopic atom into an achiral glycine substrate before further synthetic manipulation to afford the desired enantiopure deuterated α-amino acid. There are several other methods used for the stereoselective introduction of deuterium, including approaches based upon resolution of racemates, enantioselective catalysis or the use of chiral auxiliaries. (Scheme 4.4.1.)



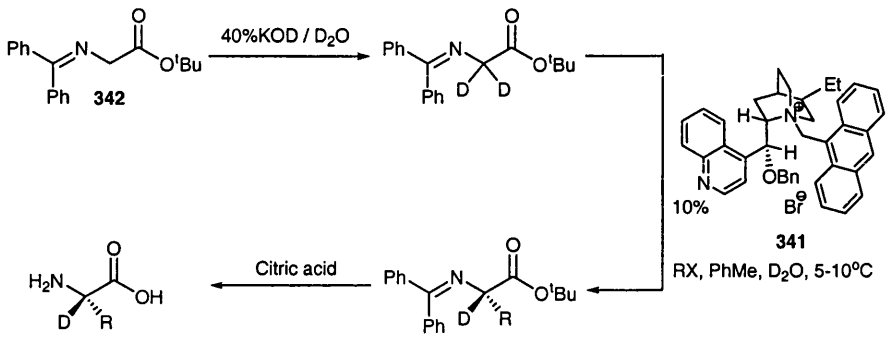

**Scheme 4.4.1.** Synthesis of α-deuterated α-amino acids.

The employment of a resolution approach allows traditional achiral methodologies such as the Strecker synthesis to be used to prepare α-deuterated α-amino acids before a subsequent resolution step to afford enantiopure isotopically labelled α-amino acids. For example, Schwoen *et al.* showed that porcine kidney acylase I could selectively hydrolyse the acetyl group of the L-enantiomer of a range of *N*-protected amino acids, allowing facile separation of the enantiomers *via* fractional crystallisation.[169] (Scheme 4.4.2.)



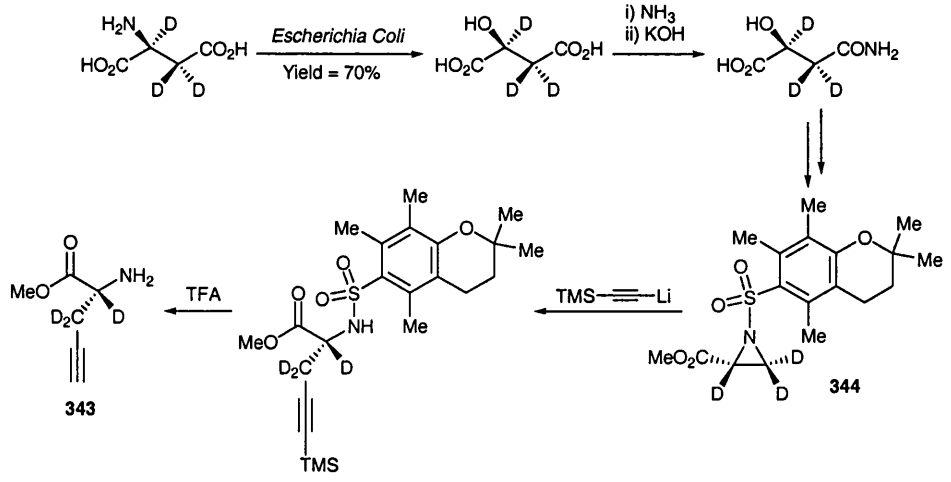

**Scheme 4.4.2.** Enzymatic resolution of α-deuterated α-amino acids.

Chiral catalysis represents a desirable synthetic route due to the small number of steps that the isotopically labelled compound must undergo before isolation. For example, Lygo *et al.* has demonstrated the use of a chiral phase transfer catalyst **341** for the catalytic production of isotopically labelled amino acids,[170] *via* enantioselective alkylation of the enolate of a preformed *bis*-deuterated Schiff base **342**. (Scheme 4.4.3)



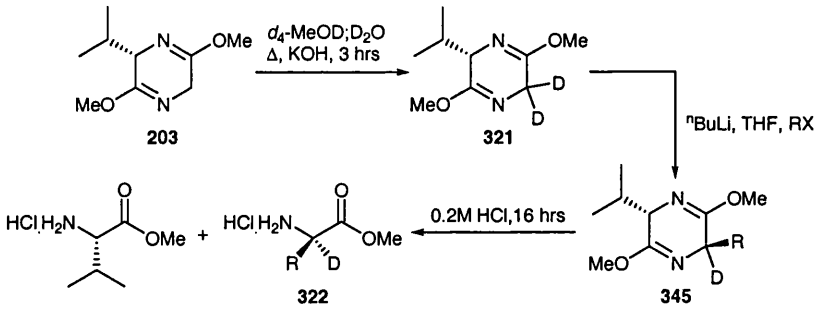

**Scheme 4.4.3.** Formation of α-deuterated α-amino acids through Lygo's phase transfer methodology.

Stereoselective synthesis represents a desirable pathway as it affords enantiopure products, however the isotopically labelled building blocks often represent challenging synthetic targets in their own right. In 1998 Young *et al.* published work detailing the synthesis of both isomers of α-deuterated α-propargyl glycine **343** during work aimed at uncovering the mechanism of oxidation of propargyl glycines with an oxidase.[171] This was achieved through nucleophilic attack of TMS-protected propargylated anion on enantiopure isotopically labelled aziridines **344**. This isotopically labelled aziridine **344** was synthesised *via* Hofmann rearrangement of a monoamide derived from isotopically labelled malic acid, itself formed from treatment of dideuterated enantiopure aspartic acid with *Escherichia Coli.*[172] (Scheme 4.4.4.)




**Scheme 4.4.4.** Formation of α-deuterated α-propargyl amino esters through ring opening of the corresponding aziridine.

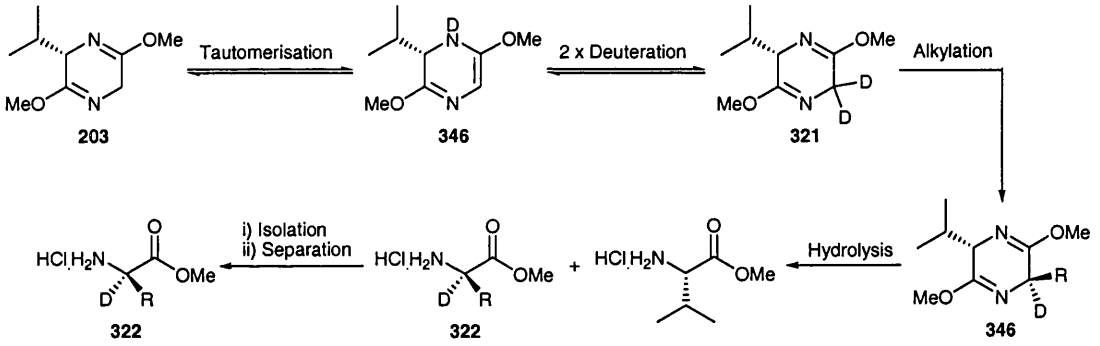
Schöllkopf's chiral auxiliary methodology has been used previously to great effect for the synthesis of enantiopure α-deuterated α-amino acids.[173, 174] Gani *et al.* reported base-catalysed incorporation of two atoms of deuterium into the $C_6$ position to afford enantiomeric *bis*-deuterated auxiliary **321**, whose *aza*-enolate was alkylated to afford its corresponding isotopically labelled *trans*-3,6-dialkyl *bis*-lactim ether **345**. Acidic cleavage then afforded its corresponding enantiopure isotopically labelled α-amino ester **322** in good yield. (Scheme 4.4.5.)




**Scheme 4.4.5.** Deuteration and alkylation of Schöllkopf's *bis*-lactim ether **321**.

## 4.4.3. A new strategy for the synthesis of isotopically labelled *bis*-lactim ether 321

As described it was proposed that access to *bis*-deuterated *bis*-lactim ether **321** might also occur under mild acidic conditions in the presence of a suitable deuterium source. Therefore, it was proposed that deuterium might be selectively introduced into the $C_6$ position of the labile *bis*-lactim ether *via* acidic equilibration of the *bis*-lactim ether **203** to its enamine form **346** in deuterated media. It was reasoned that the presence of the sterically demanding $^{i}$propyl unit at $C_3$ would prove sufficient to prevent deuterium incorporation at this position, as witnessed previously for α-alkyl valerolactim ether substrates described in section 4.2.1. Subsequent formation of the *aza*-enolate of **321**, and its reaction with an electrophile would afford the *trans*-alkylated auxiliary **345**,[117, 118] that would then be purified and cleaved to afford the desired α-amino methyl ester **322** containing a deuterium label at its α position. (Scheme 4.4.6.)

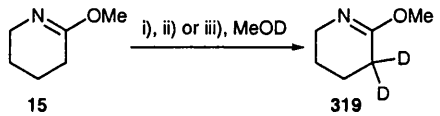



**Scheme 4.4.6.** Incorporation of deuterium into the $C_6$ position of Schöllkopf's *bis*-lactim ether **203**.

Given that Schöllkopf's methodology is one of the most widely used protocols for the synthesis of enantiopure α-amino acids it was proposed that this practical simple protocol would provide a useful tool for the synthesis of deuterated analogues due to the ease with which the isotopic label could be introduced, coupled with the effectiveness of the original methodology.

## 4.4.4. Preparation of *bis*-deuterated lactim ethers

As previously stated in this chapter, deuterium was incorporated into the α-position of valerolactim ether **15**, when it was dissolved in deuterated methanol and allowed to stand for several weeks. As a consequence, synthesis of *bis*-deuterated valerolactim ether **319** was attempted under acidic, neutral and basic conditions in an attempt to identify conditions that would rapidly drive the reaction to completion. These deuteration reactions were carried out by stirring a solution of the lactim ether in $d_1$-methanol for 24 hours, either with 20 mol% trifluoroacetic acid, or with 20 mol% sodium methoxide (generated *in situ* by addition of sodium hydride). $d_1$-Methanol was selected over $d_4$-methanol owing to its lower cost as well as the fact that a transesterification reaction would also occur under these conditions, which would also lead to unwanted incorporation of a $d_3$-methoxy fragment into the lactim ether product. (Scheme 4.4.7.)




**15** **319**

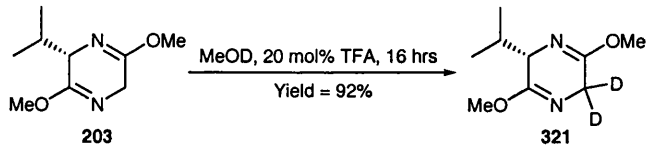
i) 20 mol% TFA, ii) 20 mol% NaOMe, iii) pH 7

**Scheme 4.4.7.** *Bis*-deuteration of valerolactim ether **15** under acidic conditions.

The $^1$H NMR spectra of these test reactions revealed that deuterium incorporation at the α-position of valerolactim ether **319** had reached a level of >97% after 16 hours in the acidic catalysed example, where as for the neutral and base catalysed reactions no deuterium incorporation had occurred.

## 4.4.5. Preparation of *bis*-deuterated *bis*-lactim ether auxiliary 321

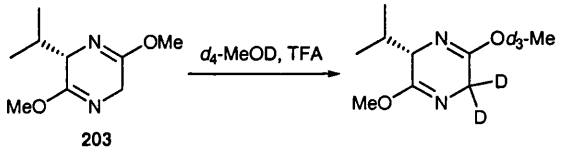
Following the precedent of the deuterium incorporation study using valerolactim ether **15** as a model substrate, it was found that treatment of *bis*-lactim ether auxiliary **203** under the same acidic conditions resulted in incorporation of two deuterium atoms in very high yield.




**Scheme 4.4.8.** Deuteration of *bis*-lactim ether **215**.

$^1$H NMR spectroscopic analysis of the resultant *bis*-deuterated *bis*-lactim ether **321** in $CDCl_3$ revealed complete loss of the resonances relating to the two diastereomeric $C_6$ ring protons, which had previously overlapped the $H_3$ proton, that now appeared as a well resolved doublet with 1H intensity at δ 3.92 (d, *J* 3.5 Hz). Likewise, the $^{13}$C NMR spectrum of **321** only displayed eight resonances, failing to exhibit a carbon resonance for the $C_6$ carbon, due to quadrapole relaxation because of the presence of the deuterium atoms.

Also worthy of note, when the deuteration reaction was repeated in $d_4$-methanol it was found that incorporation of a $d_3$-MeO fragment was only observed at the $C_5$ position, thus enabling the two methoxy resonances in the $^1$H NMR spectrum of *bis*-lactim ether **203** to be distinguished as $C_2$-OMe at δ 3.65 (s) and $C_5$-OMe at δ 3.61 (s). (Scheme 4.4.9.)

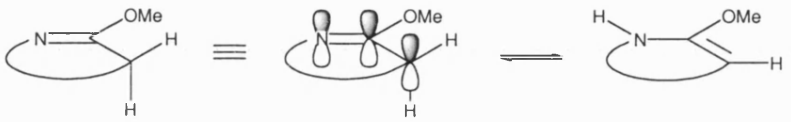



**Scheme 4.4.9.** Deuterium incorporation into the two $H_6$ protons and the methoxy unit of *bis*-lactim ether **203**.

Analysis of the specific rotation of bis-deuterated *bis*-lactim ether **321** revealed an $[\alpha]_D^{25}$ of 105.1 (*c* 1.0 in EtOH), that compared favourably with the $[\alpha]_D^{25}$ of 108.9 (*c* 1.0 in EtOH)[130] for the parent *bis*-lactim ether, further indicating that racemisation had not occurred *via* deuterium incorporation at the $C_3$ position. Finally the mass spectrum recorded for this deuterated *bis*-lactim ether **321** revealed the presence of two deuterium atoms at 187.1409.

## 4.4.6. Explanation for the lack of racemisation observed *via* a coplanar model

All physical and spectroscopic data recorded for the formation of *bis*-deuterated Schöllkopf's *bis*-lactim ether auxiliary under acidic conditions implied that no racemisation or deuterium incorporation had occurred at its $C_3$ stereocentre during incorporation of deuterium into the $C_6$ position. It is proposed that this regiocontrol could be explained using a similar 'coplanar' argument previously developed in section 2.4.2. to explain the differing reactivity of lactim ethers towards alkyl lithiums. Therefore, in order for the enamine form of a lactim ether to be accessed, it requires that one of its α-protons adopts a conformation with its σ-bond coplanar to the π orbital of its proximal imidic bond. (Scheme 4.4.10.)




**Scheme 4.4.10.** Alignment of the α-proton with the π orbitals of the imidic bond in order for the enamine tautomer may be adopted.

It is known that *bis*-lactim ether **203** adopts a conformation in which its ring system adopts a half boat conformation, with its $C_3$ $^{i}$propyl group occupying a rigid pseudo-axial orientation.[175, 176] This, in turn fixes the $C_3$ proton on a pseudo-equatorial conformation which cannot align its σ-orbital with the π-orbital of the $N_1$-$C_2$ imidic bond for enolisation to occur, and therefore deuterium incorporation does not occur at the $C_3$ position. In contrast, there is significant conformational flexibility at the $C_6$ position of the *bis*-lactim ether **203**, which demonstrates sufficient conformational lability to enable both $C_6$-H σ-bonds to overlap with the $N_4$-$C_5$ imidic bond to enable *bis*-deuteration at the $C_6$ position. (Figure 4.4.11.)

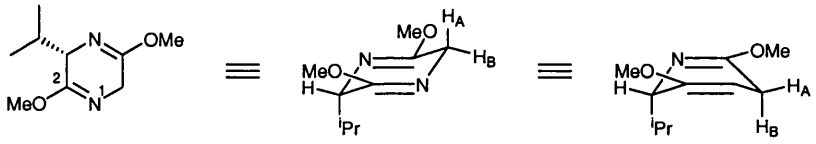
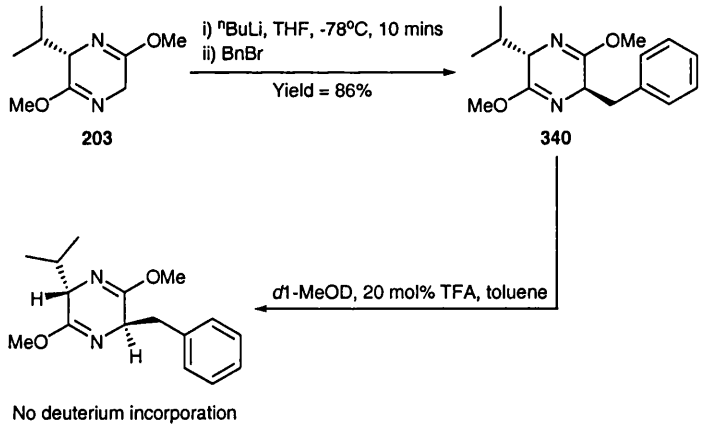


**Figure 4.4.11.** Conformers adopted by Schöllkopf's *bis*-lactim ether **203** that allows selective deuterium incorporation at the $C_6$ position.

## 4.4.7. Further investigation of the coplanar model

In order to provide further evidence for this 'coplanar' model of deuteration, a sample of *trans*-benzylated *bis*-lactim ether **340** was prepared *via* treatment of lactim ether **203** with $^{n}$BuLi in THF at -78 °C followed by addition of benzyl bromide. It was found that treatment of this *trans*-benzylated *bis*-lactim ether **340** with 20 mol% TFA in $d_1$-methanol solution for 7 days failed to produce any incorporation of deuterium at either the $C_3$ or $C_6$ positions. Therefore, the *trans*-diaxial conformation adopted by this lactim ether is sufficiently rigid to ensure no deuterium incorporation, because the $C_3$ and $C_6$ protons are unable to adopt the required pseudo axial environments. (Scheme 4.4.12.)



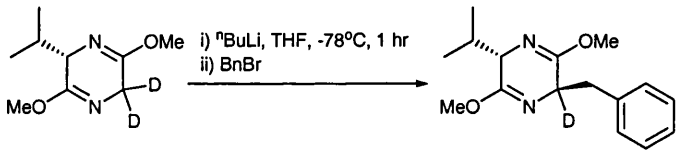

**Scheme 4.4.12.** Attempted deuteration of *trans*-benzylated *bis*-lactim ether **340**.

# 4.5. Synthesis of enantiopure α-deuterated phenylalanines

Having demonstrated formation of **321** in high yield, attention shifted to alkylation of its *aza*-enolate in order to confirm the usefulness of this methodology for the asymmetric synthesis of isotopically labelled enantiopure α-amino acids.

## 4.5.1. Synthesis of (3*S*,6*R*)-6-benzyl-6-deuterated-3,6-dihydro-3-isopropyl-2,5-dimethoxypyrazine

Benzyl bromide was initially chosen as an electrophile for the alkylation of the *aza*-enolate of *bis*-lactim ether **321**, since I already had access to non-deuterated *trans*-benzyl *bis*-lactim ether **340** for comparative purposes. The *aza*-enolate alkylation conditions employed were a modification of Schöllkopf's original conditions, involving deprotonation of the *bis*-lactim ether **321** with $^{n}$BuLi in THF for one hour at -78 °C prior to addition of 1.3 equivalents of benzyl bromide.[126] The *bis*-lactim ether **321** was deprotonated for one hour before addition of benzyl bromide in anticipation of any deuterium effect that might be operating during the deprotonation step. Under these conditions *trans*-benzyl *bis*-lactim ether **347** was formed cleanly in good yield and >95% d.e., which was purified to homogeneity by column chromatography to afford a single diastereomer in an overall 80% yield. (Scheme 4.5.1.)

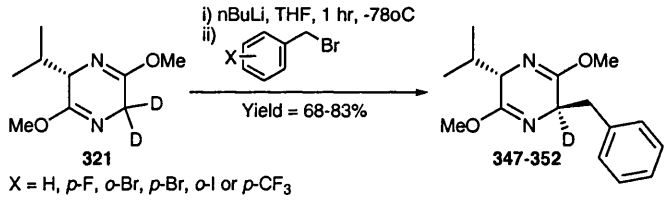


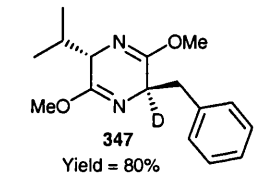

**Scheme 4.5.1.** *Trans*-alkylation of the *aza*-enolate of *bis*-lactim ether **321** with benzyl bromide.

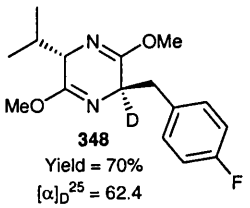
Analysis of the $^{1}$H NMR spectrum of *trans*-benzyl *bis*-lactim ether **347** revealed it to be identical to that recorded previously for the non-deuterated derivative **340**, except for the absence of the $C_6$-proton at δ 3.89-3.97, and simplification of the ABX quartet relating to the benzylic methylene protons to a simple resonance, δ 2.99 (2H, app s). Importantly, the intensity of the integral for the $C_3$-proton was equivalent to one proton,

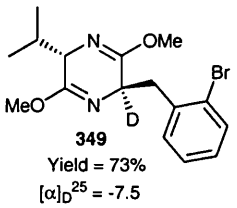
indicating that no deuterium (or racemisation) had occurred at this stereocentre in the previous deuteration step. The $^{13}C$ NMR spectrum of **347** revealed the expected 13 resonances, with no resonance being observed for the $C_6$ position owing to the large NOE effect from the neighbouring quadripolar deuterium nucleus, whilst the molecular ion of 276.1814 revealed that a single deuterium atom was present in the molecule.

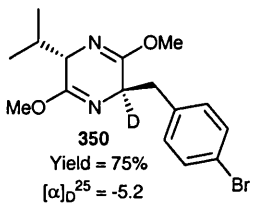
Given the success of this *aza*-enolate benzylation protocol, it was decided to prepare a series of 6-deuterated *bis*-lactim ethers containing different halogen substituents in their aryl ring. Therefore, treatment of the *aza*-enolate of *bis*-deuterated *bis*-lactim ether **321** with a series of five different electrophiles afford *trans*-alkylated *bis*-lactim ether **348-352** in >90% d.e., that were purified by column chromatography to >95%. (Figure 4.5.1.) It was pleasing to note that the $[\alpha]_D^{25}$ reading for the *trans*-benzyl *bis*-lactim **347** ether matched that previously reported by Gani *et al.*[173]

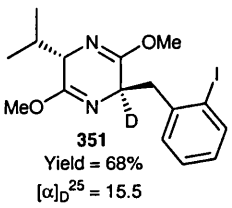


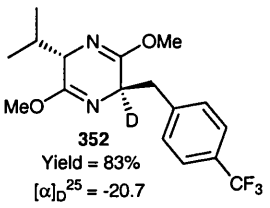
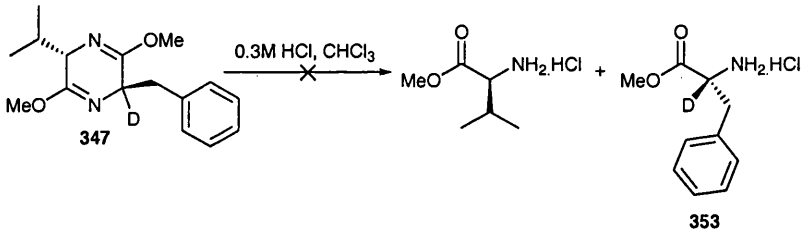




**Figure 4.5.1.** *Trans*-alkylated *mono*-deuterated Schöllkopf's *bis*-lactim ethers **347-352.**

All compounds were fully characterised and demonstrated spectroscopic and physical data consistent with the formation of *trans*-benzylated *bis*-lactim ethers that were *mono*-deuterated at their $C_6$ position.

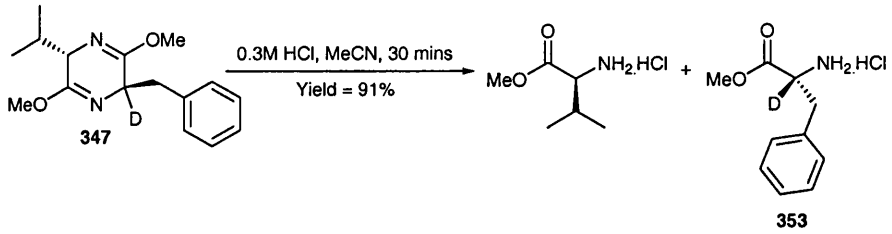
## 4.5.2. Preparation of α-deuterated (*R*)-phenylalanines

Initial attempts to hydrolyse *trans*-benzylated *bis*-lactim ether **347** employed the conditions previously developed for hydrolysis of α-alkyl valerolactim ethers described in section 2.5.1. However, this approach was unsuccessful, failing to afford a clean hydrolysis reaction pathway to α-deuterated (*R*)-phenylalanine methyl ester **353**, with large amounts of starting *trans*-benzylated *bis*-lactim ether **347** being recovered. (Scheme 4.5.2.)



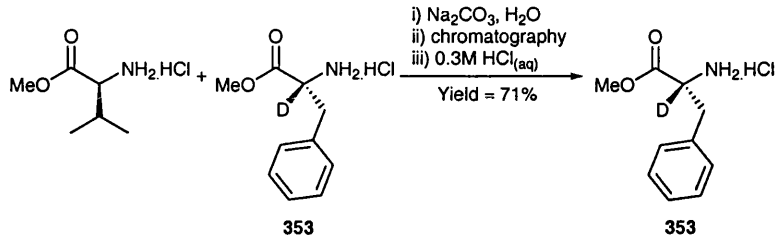

**Scheme 4.5.2.** Unsuccessful hydrolysis of **347**.

A review of literature precedent revealed that the use of acetonitrile as a polar organic cosolvent had proven successful for the hydrolysis of related *bis*-lactim ethers.[177-180] Therefore, a solution of *bis*-lactim ether **347** in a 1:1 mixture of acetonitrile:0.5M $HCl_{(aq)}$ was rapidly stirred for 30 minutes to afford a quantitative mixture of L-valine methyl ester and α-deuterated phenylalanine methyl ester **353** as their hydrochloride salts. (Scheme 4.5.3.)




**Scheme 4.5.3.** Hydrolysis of *bis*-lactim ether **347** to afford α-deuterated phenylalanine methyl ester **353**.

Separation of the two α-amino esters was achieved *via* column chromatography of the free amines, generated by treatment of the crude reaction mixture with sodium hydrogen carbonate. This afforded α-deuterated (*R*)-phenylalanine methyl ester **353** as its free amine, which was reacidified with 0.5M HCl solution to afford the more stable α-deuterated phenylalanine methyl ester hydrochloride salt in 71% overall yield from the *trans*-benzylated *bis*-lactim ether **347**. (Scheme 4.5.4.)




**Scheme 4.5.4.** Isolation of α-deuterated (*R*)-phenylalanine **353**.

The $^1H$ NMR spectrum of **353** matched that of an authentic sample of phenylalanine methyl ester except for the expected loss of the proton resonance at the α-position and simplification of the ABX mulitplet of the benzylic methylene protons to an AB quartet δ 3.24 (d, *J* 14.0 Hz) and δ 3.25 (d, *J* 14.0 Hz). (Figure 4.5.2.)

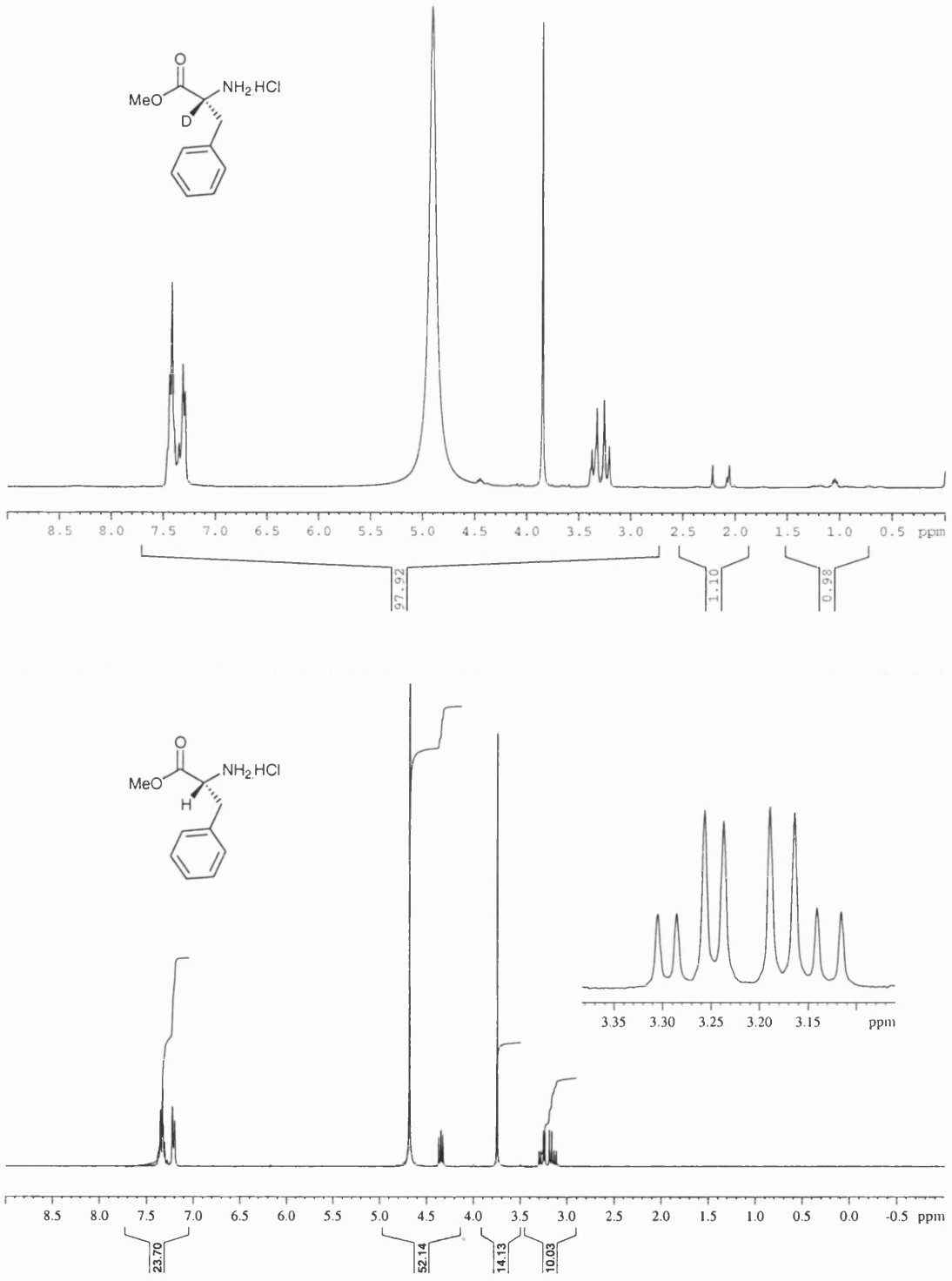



**Figure 4.5.2.** $^{1}H$ NMR spectra of deuterated **353** and non-deuterated phenylalanine methyl esters.

The $^{2}D$ NMR spectrum of α-deuterated (*R*)-phenylalanine methyl ester revealed a resonance for the deuterium atom at δ 4.22 (bs), at the same chemical shift observed for the α-proton of phenylalanine methyl ester in its $^{1}H$ NMR spectrum. The $^{13}C$ NMR

spectrum afforded six resonances again failing to show a resonance for the deuterated centre. This hydrolysis reaction was then repeated for the five further *trans*-benzylated *bis*-lactim ethers **348-352** to afford a range of six α-deuterated (*R*)-substituted phenylalanines **354-358** that were converted into their free amines and separated from L-valine methyl ester by column chromatography. Conversion of these α-amino esters to their hydrochloride salts afforded compounds with spectroscopic data consistent with formation of enantiopure α-deuterated phenylalanine methyl esters. It was particularly pleasing to find that specific rotation values of the three previously reported enantiopure phenylalanine methyl esters **354** and **358**[5] matched well with the data reported previously for these non-deuterated α-amino esters.[173, 181, 182] (Figure 4.5.5.)

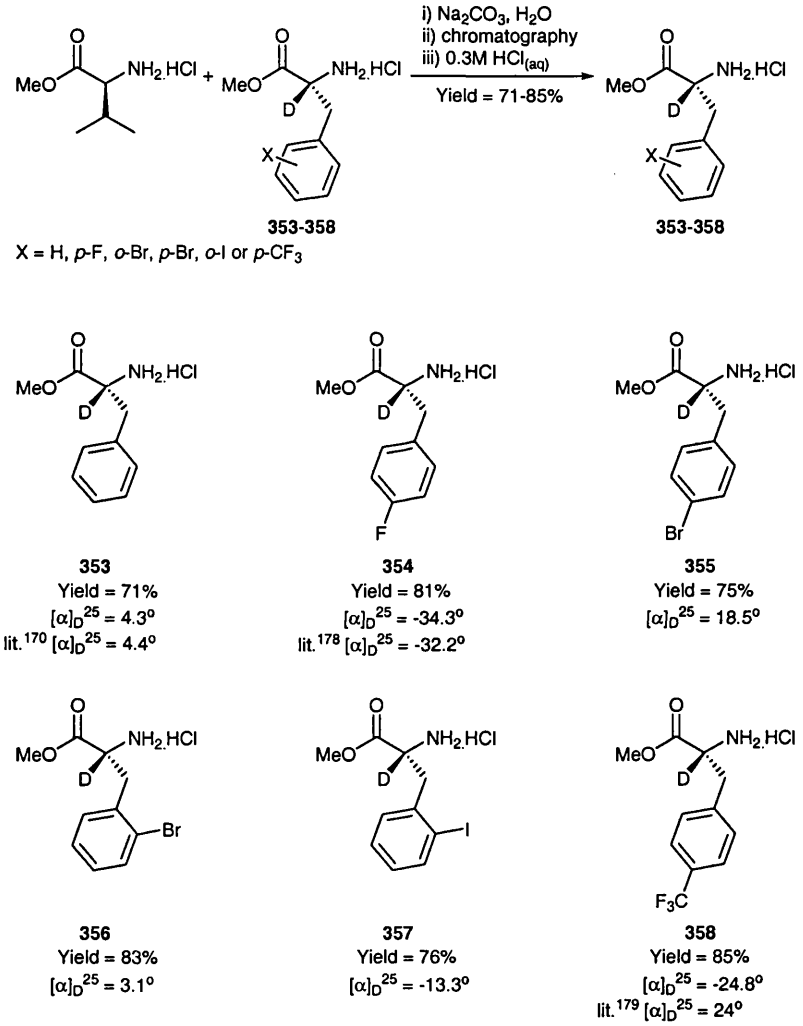



**Figure 4.5.5.** Structures of the synthesised enantiopure α-deuterated amino esters **353-358**.

[5] Comparison to the non-deuterated and opposite enantiomers.[170,178,179]

### 4.5.3. Enantiomeric excess determination *via* the use of (*S*)-BINOL-boronate chiral derivitisation agent

The enantiomeric excess of (*R*)-α-deuterated phenylalanine **347** was confirmed through the employment of the (*S*)-BINOL-boronate-imine chiral derivatising agent previously described in section 3.4.2. In order to allow for comparative studies authentic boronate-imine complexes of racemic phenylalanine methyl ester **359** and (*R*)-phenylalanine-(*S*)-BINOL **360** were also formed. Analysis of the $^{1}$H NMR spectrum of the complex derived from (*R*)-α-deuterated phenylalanine methyl ester **361** showed that there was a single pair of resonances relating to the benzylic methylene protons at δ 2.96 (d, *J* 14.0 Hz) and δ 3.27 (d, *J* 14.0 Hz), with a single resonance corresponding to the methyl ester group δ 3.70 (s) and a singlet for the imine proton at δ 7.92 (s). Comparison with the $^{1}$H NMR spectra of the complexes formed from *rac*-phenylalanine methyl ester **359** and (*R*)-phenylalanine methyl ester **360** demonstrated that the *mono*-deuterated (*R*)-phenylalanine methyl ester **353** had been formed in enantiopure form and had not undergone racemisation of the α-centre. Therefore, this observation provides further evidence that no racemisation of the *bis*-lactim ether **321** had occurred during its deuteration with $d_1$-methanol under acidic conditions. (Figure 4.5.3. and 4.5.4.)

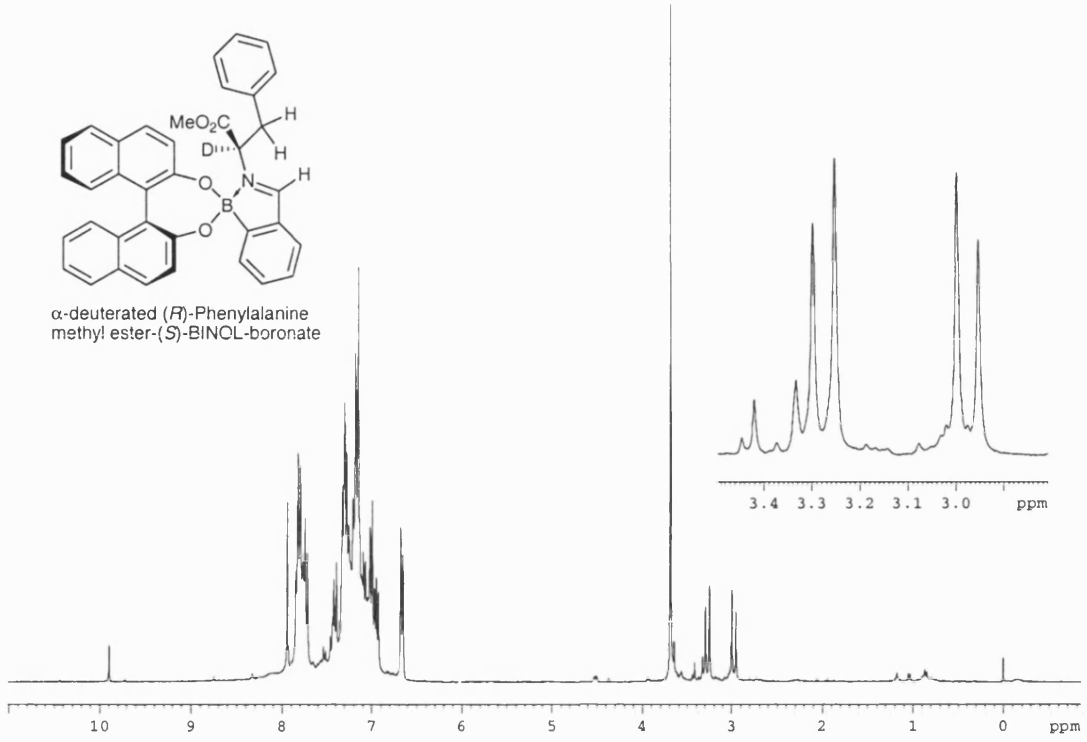



**Figure 4.5.3.** $^{1}$H NMR spectrum of α-deuterated (*R*)-phenylalanine methyl ester **361**-boronate-imine complex.

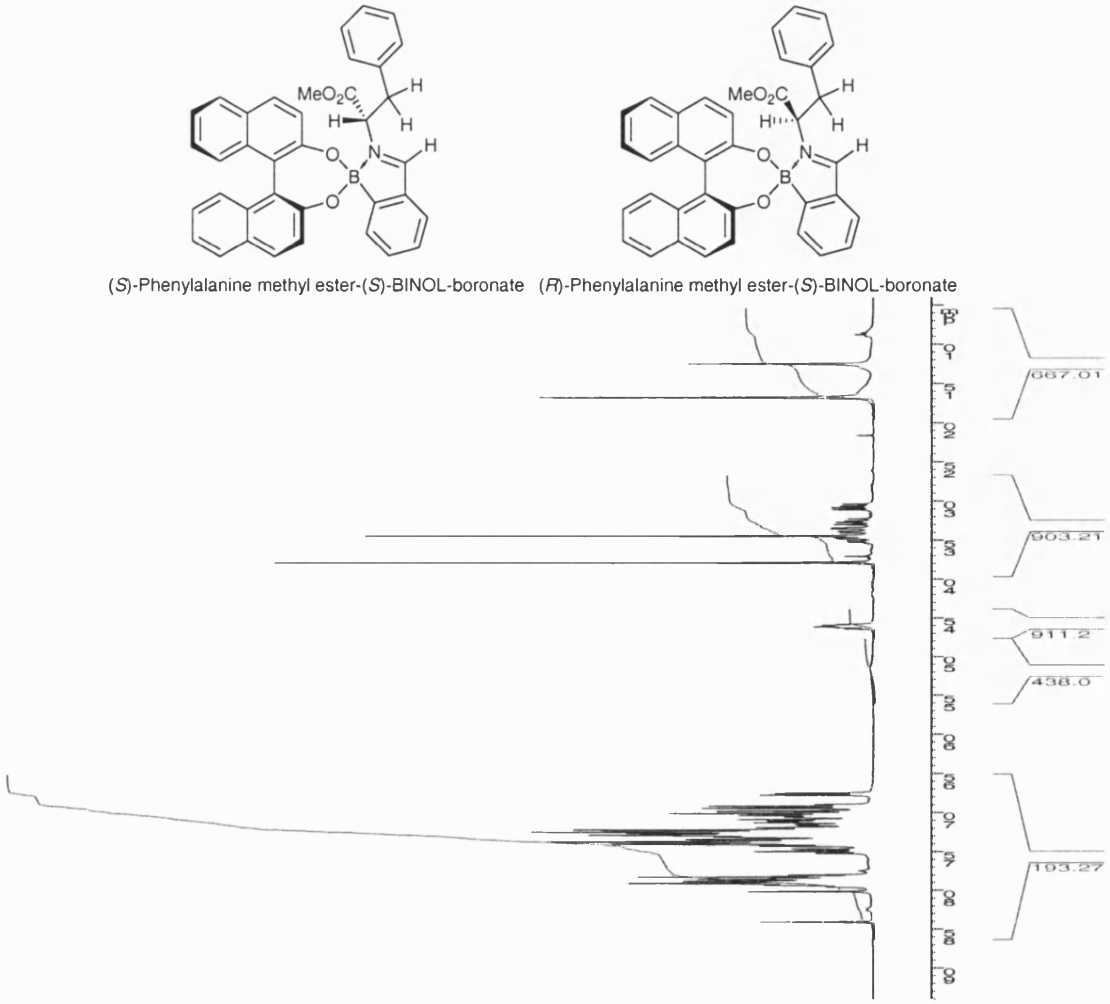



**Figure 4.5.4.** $^{1}$H NMR spectrum of *rac*-phenylalanine methyl ester **359**-boronate-imine complexes.

## 4.6. Conclusion

This section of the thesis has detailed work relating to the formation of orthogonally protected *bis*-lactim ethers for the formation and facile separation of enantiopure α-amino esters.

It has also detailed work showing that deuterium can be readily and regioselective incorporated into the $C_6$ position of *bis*-lactim ether **230** under mild conditions, and that the resultant deuterium labelled *bis*-lactim ether **321** can be used for the asymmetric synthesis of enantiopure α-deuterated α-amino esters.

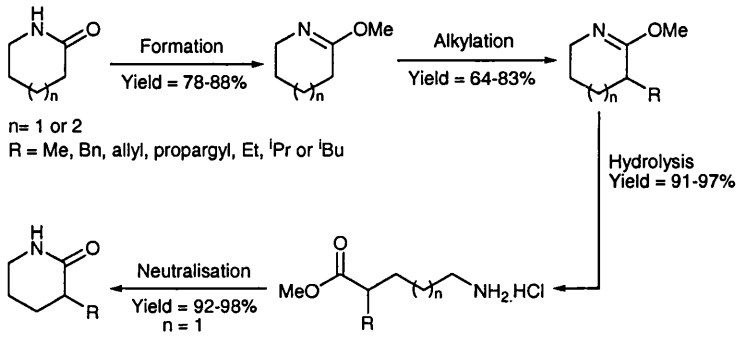
# Chapter 5

# Summary

# 5.1. Summary

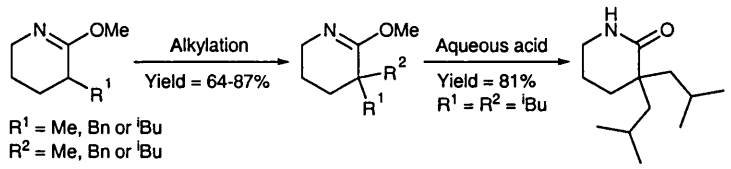
In chapter 1 of this thesis the synthetic versatility of imino and lactim ethers was demonstrated, with particular reference made to their applicability in the field of heterocyclic chemistry and in turn to the arenas of drug discovery and natural product synthesis.

The second chapter described the development of methodology relating to the formation of the *aza*-enolates of lactim ethers, for the ensuing production of α-alkyl analogues. The methodology reported herein proceeded in high and reliable yields with a wide variety of substrates. The applicability of this methodology for the synthesis of a wide range of α-alkyl lactim ethers, α-alkyl ω-amino esters and α-alkyl valerolactams was demonstrated. (Scheme 5.1.1.)



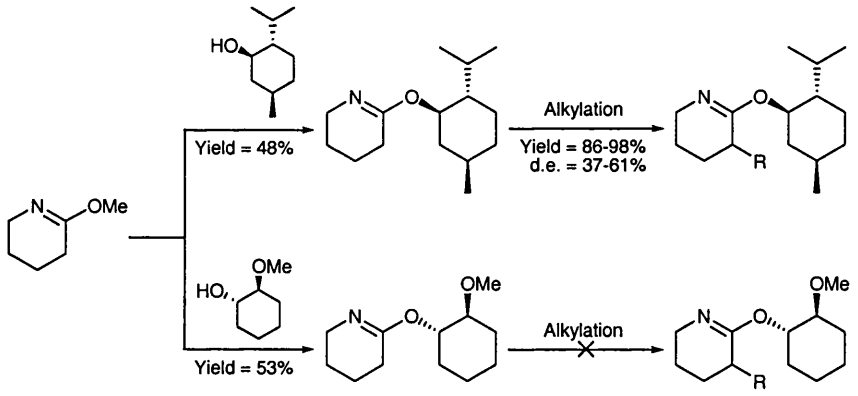

**Scheme 5.1.1.** Overview of the alkylation of the *aza*-enolates of valero and caprolactim ethers, with the ensuing hydrolysis and neutralisation reactions to afford the α-alkyl valerolactams.

In the case of valerolactim ether it was further shown that the *aza*-enolate of an α-alkyl valerolactim ether could also be alkylated in good yield, however the resultant compounds did not undergo hydrolysis to the corresponding α-alkyl ω-amino esters, instead directly forming the di-alkyl valerolactams. (Scheme 5.1.2.)




**Scheme 5.1.2.** Alkylation of the *aza*-enolate of α-alkyl valerolactim ethers, and subsequent lactam formation of the di-$^{i}$butyl valerolactim ethers

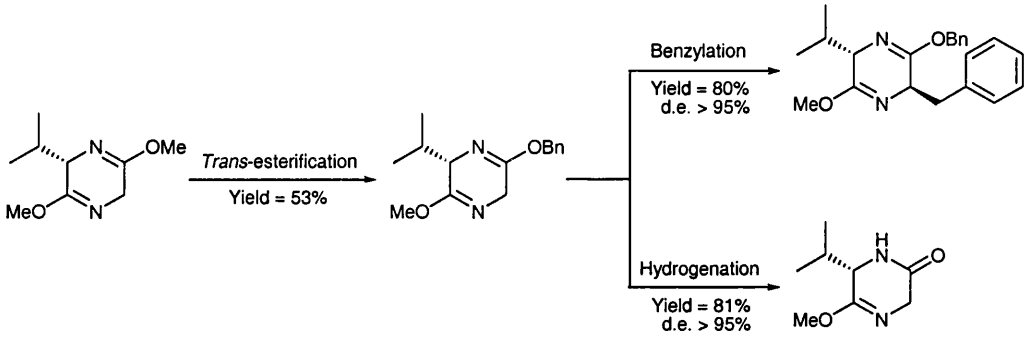
Given the positive results in the racemic series, chapter 3 of this thesis concentrated on the development of analogous chiral systems through the use of chiral auxiliaries and chiral ligands. In the first case transesterification methodology was developed to afford a reliable route to valerolactim ethers containing chiral alcohol fragments (-)-menthol and (1*S*,2*S*)-2-methoxycyclohexanol. However, the diastereoselectivity obtained for alkylation of the *aza*-enolate of the (-)-menthol valerolactim ether proved unsatisfactory, furthermore the major diastereomer could not be purified to homogeneity. Alternatively, the (1*S*,2*S*)-2-methoxycyclohexanol derived valerolactim ether did not afford products arising from alkylation of its *aza*-enolate but instead reacted with butyl lithium to afford an imine product. (Scheme 5.1.3.)




**Scheme 5.1.3.** Transesterification of valerolactim ether with chiral alcohols and ensuing alkylation of the (-)-menthol valerolactim ether.

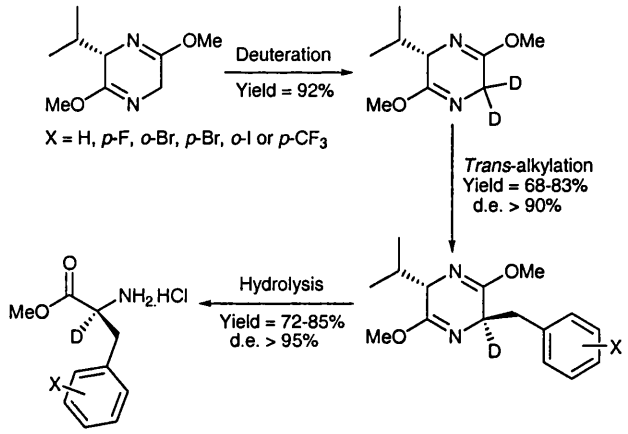
The final chapter of work within this thesis detailed research relating to two extensions to Schöllkopf's *bis*-lactim ether methodology. The first piece of research described the formation of an orthogonally protected *O*-methyl *O*-benzyl *bis*-lactim ether, that once *trans*-alkylated and hydrolysed would have had the potential for facile separation of the

amino esters formed through simple hydrogenation of the resultant α-alkyl benzyl amino ester to the corresponding α-alkyl amino acid. Further to this it was shown that this substrate offered ready access to *mono*-lactim ether species, that upon hydrolysis allowed access to enantiopure dipeptides. Unfortunately work in the area was curtailed through the moderate yields obtained during synthesis of the orthogonally protected *bis*-lactim ether. (Scheme 5.1.4.)




**Scheme 5.1.4.** Formation of an orthogonally protected *bis*-lactim ether and alkylation of its *aza*-enolate and hydrogenation to it *mono*-lactim species.

Concurrently to this orthogonal protection research another extension to this class of methodology was developed relating to the regioselective incorporation of a deuterium atoms into the auxiliary under mild conditions. The resultant isotopically labelled *bis*-lactim ether was employed for the synthesis of a range of (*R*)-phenylalanines that were isolated in high yield. (Scheme 5.1.5.)




**Scheme 5.1.5.** Deuteration, subsequent alkylation and hydrolysis of the *aza*-enolate of Schöllkopf's *bis*-lactim ether to afford a range of isotopically labelled (*R*)-phenylalanine hydrochlorides.

# Chapter 6

# Experimental data

"...long is the way, and hard
That out of Hell leads up to light..."

*Paradise Lost,* II, 432-3

# Chapter 6. Experimental

## 6.1. General conditions

Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter. Infra red spectra were recorded in the range 4000-600 $cm^{-1}$ on a Perkin Elmer FT 1605 spectrometer using KBr plates with internal calibration. $^1H$ NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 MHz. Chemical shifts ($\delta$) are expressed in parts per million (ppm), and are relative to residual protic solvent $CHCl_3$ ($\delta_H$ 7.26), $CH_3OD$ ($\delta_H$ 3.31) or tetramethyl silane ($\delta_H$ 0). The multiplicities are presented in the following manner:

-singlet, s
-broad singlet, bs
-doublet, d
-triplet, t
-quartet, q
-septet, sept
-multiplet, m
-broad multiplet, bm
-apparent, app

Coupling constants (*J*) are measured in Hz. Diastereomeric excesses were measured from GCMS spectra or the relative intensities of the relevant peaks in the $^1H$ NMR spectra unless otherwise stated. $^{13}C$ NMR spectra were recorded in $CDCl_3$, MeOD, $D_2O$, at 75 MHz using the resonance of $CDCl_3$ ($\delta_C$ = 77.1, t) or $d_4$-methanol ($\delta_C$ = 49.0, sept) as the internal reference.

Gas Chromatography Mass spectra were carried out at the University of Bath (Hewlett Packard 5890 and Hewlett Packard 5970) and accurate mass spectra were carried out at the University of Wales, Swansea (Finnigan MAT 900 XLT) using electron ionisation (EI) and chemical ionisation (EI) techniques.

Single crystal X-ray diffraction data were collected on a Nonius Kappa CCD machine. Structural determination and refinement were achieved using the SHELZ suite of programmes; drawings were produced using ORTEX.

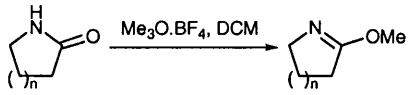
Analytical thin layer chromatography was performed on precoated aluminium backed silica gel (Machery Nagel Alugram SII G/$UV_{254}$) plates. Plates were visualised under ultra violet light (at 254 nm) or by staining with potassium permanganate, vanillin or phosphomolybdic acid before heating. Column chromatography was carried out using Merck Kieselgel 60H silica gel. Samples were added to the top of the column preabsorbed onto either silica or magnesium sulfate.

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from $CaH_2$ under nitrogen. Petrol refers to light petroleum, bp 40-60 °C and was distilled without drying.

Commercially available starting materials were obtained from Avocado, Sigma-Aldrich, Merck, Lancaster, Acros or Fluka and were used throughout without further purification. Reactions requiring anhydrous conditions were performed under nitrogen in oven or flame dried apparatus.

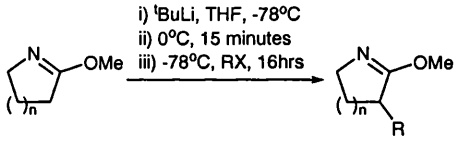
# 6.2. General procedures

## General protocol A



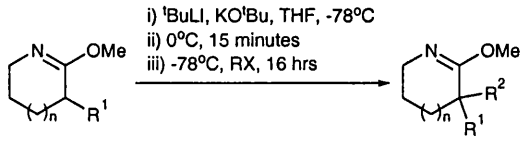

Trimethyloxonium tetrafluoroboronate (1.1 eq.) was added directly to a stirred solution of the corresponding lactam (1 eq.) in DCM at room temperature under a nitrogen atmosphere and allowed to stir for 18 hours. Solid $K_2CO_3$ (1.5 eq.) was added and the reaction stirred until the reaction mixture ceased effervescence, saturated $K_2CO_3$ was then added and the reaction mixture stirred for a further 5 minutes, before being diluted with distilled water and DCM. The organic phase was extracted with DCM (x 3). The combined organic extracts were washed with dilute $K_2CO_3$ (x 3), dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding *O*-methyl lactim ether.

## General procedure B



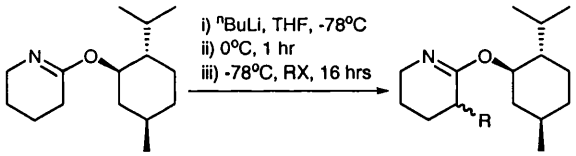

A solution of $^t$BuLi in hexanes (1.5 eq.) was added dropwise to a stirred solution of lactim ether (1 eq.) in THF at –78 °C under a nitrogen atmosphere, the reaction mixture was then allowed to warm to room temperature and to stir for 15 minutes before being cooled to –78 °C. The corresponding electrophile was then added dropwise to the stirred solution and allowed to warm to room temperature over 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (x 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* before undergoing Kügelrohr distillation to afford the corresponding α-alkyl lactim ether.

## General procedure C



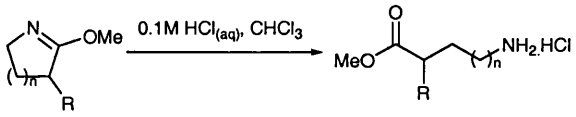

A solution of $^{t}$BuLi in hexanes (1.5 eq.) was added dropwise to a stirred solution of lactim ether (1 eq.) and KO$^{t}$Bu (1.5 eq.) in THF at –78 °C under a nitrogen atmosphere, the reaction mixture was then allowed to warm to room temperature and to stir for 15 minutes before being cooled to –78 °C. The corresponding electrophile was then added dropwise to the stirred solution and allowed to warm to room temperature over 16 hours. Alkaline water (>pH 8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (x 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding α-alkyl, or α,α-dialkyl lactim ether.

## General procedure D



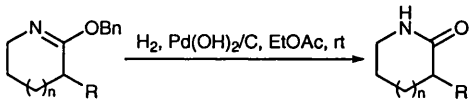

A solution of $^{n}$BuLi in hexanes (2.5 eq.) was added dropwise to a stirred solution of lactim ether **288** (1 eq.) in THF at –78 °C under a nitrogen atmosphere, the reaction mixture was then allowed to warm to room temperature and to stir for 60 minutes before being cooled to -78 °C. The corresponding electrophile was then added dropwise to the stirred solution and allowed to warm to room temperature over 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (x 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding α-alkyl (-)-menthol lactim ether.

## General protocol E



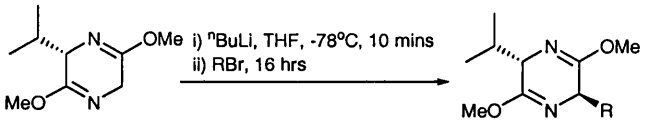

0.1M $HCl_{aq}$ (1.5 eq.) was added to a stirred solution of the corresponding lactim ether in $CHCl_3$ and the reaction mixture stirred vigorously for 16 hours. The reaction was then concentrated *in vacuo* to yield the corresponding α-alkyl ω-amino ester hydrochloride salt.

## General protocol F



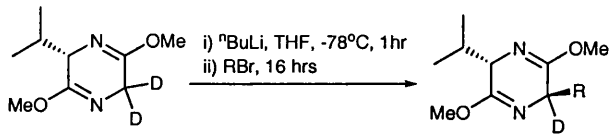

Lactim ether (1.1 eq) was stirred vigorously in the presence of palladium dihydroxide on carbon (0.15 eq) in EtOAc under an atmosphere of hydrogen for 16 hours. The reaction mixture was then dried ($MgSO_4$) filtered through Celite® and concentrated *in vacuo* to afford the corresponding lactam.

## General procedure G



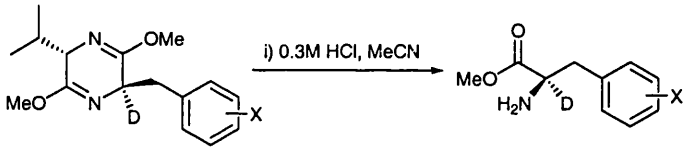

$^n$BuLi in hexanes (1.1 eq.) was added dropwise to a stirred solution of *bis*-lactim ether in THF under nitrogen at -78 °C, and the reaction mixture allowed to stir for 10 minutes at -78 °C. A solution of the electrophile (1.3 eq.) in THF was added dropwise to the above stirred solution, and the reaction mixture allowed to stir for 16 hours whilst warming to room temperature. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (x 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding *trans*-alkylated *bis*-lactim ether.

## General procedure H




$^{n}$BuLi in hexanes (1.1 eq.) was added dropwise to a stirred solution of *bis*-lactim ether in THF under nitrogen at -78 °C, and the reaction mixture allowed to stir for 1 hour at -78 °C. A solution of the electrophile (1.3 eq.) in THF was added dropwise to the above stirred solution, and the reaction mixture allowed to stir for 16 hours whilst warming to room temperature. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (x 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding *trans*-alkylated *bis*-lactim ether.

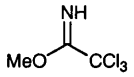
## General procedure I




*Trans*-alkylated deuterated *bis*-lactim ether (1.0 eq.) was added to a 1:1 stirred solution of 0.3M HCl (3 eq.) in MeCN and allowed to stir vigorously for 20 minutes. The reaction mixture was then concentrated *in vacuo* and neutralised with concentrated $Na_2HCO_3$ solution (1.5 eq.) before being purified by column chromatography, reacidified with 0.3M HCl (1.5 eq.) and the solvent removed *in vacuo* to afford the desired α-deuterated α-amino ester.

# 6.3. Experimental data

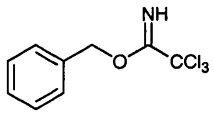
## Methyl 2,2,2-trichloroacetimidate 3[17]




3

Trichloroacetonitrile (10 ml, 100 mmol) was added to a stirred solution of methanol (6.5 ml, 200 mmol) and 60% sodium hydride in mineral oil (0.3901 g, 9.58 mmol) in DCM (100 ml) and the reaction mixture stirred for 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with DCM (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified *via* distillation to afford the title compound **3** as a clear oil (14.64 g, 83.1 mmol) in 83% yield; $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.95 (3H, s, Me), 8.28 (1H, bs, NH); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 56.2, 91.4, 163.7.

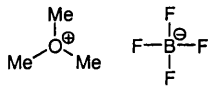
## Benzyl 2,2,2-trichloroacetimidate 4[17]




4

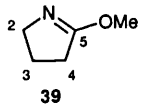
Trichloroacetonitrile (10 ml, 100 mmol) was added to a stirred solution of benzyl alcohol (13 ml, 127 mmol) and 60% sodium hydride in mineral oil (0.4275 g, 10.67 mmol) in DCM (100 ml) and the reaction mixture stirred for 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with DCM (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified *via* distillation to afford the title compound **4** as a clear oil (17.17 g, 68 mmol) in 68% yield; $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 5.35 (2H, s, $CH_2$), 7.13-7.38 (5H, bm, $H_{AR}$), 8.30 (1H, bs, N*H*).

## Trimethyloxonium tetrafluoroboronate[130]



Dimethyl ether (100 g, 2.17 mol) was condensed into a stirred solution of epichlorohydrin (10 ml, 128 mmol) in DCM (125 ml) at -78 °C under nitrogen. The reaction vessel was fitted with a dry ice condenser and the reaction mixture was warmed to -20 °C. $BF_3.OEt_2$ (10 ml, 63 mmol) was added dropwise to the reaction mixture with stirring, after the addition was complete a second aliquot of epichlorohydrin (10 ml, 128 mmol) was added and the reaction mixture stirred. This process of alternating additions was repeated 7 times in total before the reaction mixture was allowed to warm to room temperature. Filtration afforded a crude white solid that was washed with $CHCl_3$ (100 ml) to afford the title compound as a white solid (147 g, 99.9 mmol) in 92% yield.

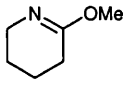
## 3,4-dihydro-5-methoxy-2H-pyrrole 39[183]



**39**

Reaction of butyrolactam **246** (21.50 g, 0.25 mol) with trimethyloxonium tetrafluoroboronate (48.61 g, 0.329 mol) in DCM (50 ml) according to general protocol A afforded the title compound **39** as a clear oil (21.06g, 0.21 mol) in 85% yield, $\nu_{max}/cm^{-1}$ 1652 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.96 (2H, app ttt, *J* 8.0, 7.0 and 1.2 Hz, 2 x H3), 2.34 (2H, *J* 8.0 and 1.2 Hz, 2 x H4), 3.59 (2H, tt, *J* 7.0 and 1.2 Hz, 2 x H2), 3.73 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 23.7, 31.2, 55.3, 55.6, 174.1; *m/z* (EI) 100.0757 ($M\text{-}H^+$ requires 100.0757) 100 (100%).

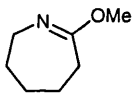
## 2,3,4,5-tetrahydro-6-methoxypyridine 15[183]




15

Reaction of valerolactam **215** (22.4 g, 0.23 mol) with trimethyloxonium tetrafluoroboronate (43.47 g, 0.29 mmol) in DCM (50 ml), according to general protocol A afforded the title compound **15** as a clear oil (23.03 g, 0.202 mmol) in 88% yield, $\nu_{max}/cm^{-1}$ 1635 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.45-1.54 (2H, bm, 2 x H4), 1.60-170 (2H, bm, 2 x H3), 2.01 (2H, dt, *J* 6.8 and 1.2 Hz, 2 x H5), 3.41 (2H, dt, *J* 5.7 and 1.2 Hz, 2 x H2), 3.55 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 20.7, 22.8, 26.2, 47.1, 52.2, 163.3; *m/z* (EI) 114.0914 ($M\text{-}H^+$ requires 114.0914) 114 (100%).

## 7-Methoxy-3,4,5,6-tetrahydro-2H-azepine 16[183]

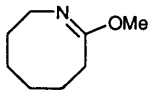



16

Reaction of caprolactam **10** (15.2 g, 0.12 mol) with trimethyloxonium tetrafluoroboronate (23.1 g, 0.16 mol) in DCM (25 ml), according to general protocol A afforded the title compound **16** as a clear oil (11.86 g, 93.3 mmol) in 78% yield, $\nu_{max}/cm^{-1}$ 1678 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.38-1.52 (4H, bm, 2 x H4 and 2 x H5), 1.62-1.72 (2H, bm, 2 x H3), 2.31 (2H, app t[6], *J* 5.7 Hz, 2 x H6), 3.32 (2H, app t[vi], *J* 4.9 Hz, 2 x H2), 3.49 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 23.8, 28.3, 31.6, 32.4, 49.0, 52.8, 170.1; *m/z* (EI) 128.1070 ($M\text{-}H^+$ requires 128.1070) 128 (100%).

[6] Second order multiplet due to magnetic inequivalence

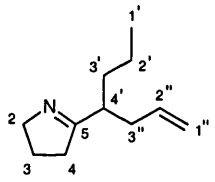
## 8-Methoxy-2,3,4,5,6,7-hexahydro-azocine 237[183]




237

Reaction of oenantholactam **243** (10.2 g, 72.2 mmol) with trimethyloxonium tetrafluoroboronate (13.90 g, 93.9 mol) in DCM (15 ml) according to the general protocol A afforded the title compound **237** as a clear oil (8.16 g, 57.8 mmol) in 80% yield; $\nu_{max}/cm^{-1}$ 1665 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.24-1.43 (4H, bm, 2 x H4 and 2 x H5), 1.46-1.65 (4H, bm, 2 x H3 and 2 x H6), 2.24 (2H, t, *J* 6.3 Hz, 2 x H7), 3.34 (2H, t, *J* 5.8 Hz, 2 x H2), 3.54 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 24.8, 26.4, 27.9, 28.3, 31.3, 47.3, 52.7, 167.4; *m/z* (EI) 140.1309 ($M\text{-}H^+$ requires 140.1070) 141 (100%).

## 5-(hept-1-en-4-yl)-3,4-dihydro-2H-pyrrole 248

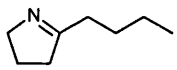



248

A solution of **39** (0.200 g, 2.02 mmol) in THF was allowed to stand in the presence of 3Å molecular sieves (0.010 g) for 15 minutes before being transferred to a *via* cannular to a second round bottomed flask. $^n$Butyl lithium (1.3 ml, 3.03 mmol) was then added dropwise to the above stirred solution at -78 °C under nitrogen, the reaction mixture was allowed to warm to room temperature and to stir for 15 minutes before being cooled to –78 °C. The allyl bromide (0.22 ml, 3.03 mmol) was then added dropwise to the stirred solution and allowed to warm to room temperature over 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified by silica gel chromatography (20% EtOAc/petrol) to afford the title compound **248** (0.39 g, 0.2365 mmol) in 12% yield as

a clear oil, $\nu_{max}/cm^{-1}$ 1640 (C=C), 1699 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.83 (3H, t, *J* 7.0 Hz, 3 x H1'), 1.12-1.22 (2H, m, 2 x H2'), 1.36-1.47 (2H, m, 2 x H3'), 1.75 (2H, app quin, *J* 7.0 Hz, 2 x H3), 2.18 (2H, app tt, *J* 7.0 and 1.1 Hz, 2 x H3''), 2.33 (2H, tt, *J* 8.2 and 1.7 Hz, 2 x H4), 2.51 (1H, app q, *J* 7.2 Hz, 1 x H 4'), 3.71 (2H, tt, *J* 7.0 and 1.7 Hz, 2 x H2), 4.90 (1H, app dq, *J* 10 and 1.1 Hz, 1 x H1''*cis*), 4.94 (1H, ddt, *J* 17.1, 1.5 and 1.5 Hz, 1 x H1''trans), 5.66 (1H, ddt, *J* 17.1, 10 and 7.2 Hz, 1 x H2''), $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 14.5, 20.9, 22.8, 35.0, 35.0, 37.7, 43.7, 60.6, 116.3, 136.9, 181.3; *m/z* (EI) 166.1590 ($M-H^+$ requires 166.1590) 166 (100%)

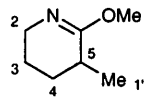
## 5-butyl-3,4-dihydro-2H-pyrrole 250[184]




250

A solution of 1.7M $^n$BuLi in hexanes (3.26 ml, 5.5 mmol) was added dropwise to a stirred solution of **39** (0.5000 g, 5.0 mmol) in THF (10 ml) at -78 °C under a nitrogen atmosphere. The reaction mixture was then allowed to warm to room temperature and stir for 15 minutes before being recooled to -78 °C and stirred for 5 minutes, water (0.3 ml, 0.17 mmol) was then added and the reaction mixture allowed to stir for 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified by silica gel chromatography (50% EtOAc/petrol) to afford the title compound **250** (0.0145 g, 0.12 mmol) in 21% yield as a clear oil; $\nu_{max}/cm^{-1}$ 1690 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.85 (3H, t, *J* 7.0 Hz, 3 x H1'), 1.27 (2H, app sept, *J* 7.0 Hz, 2 x H2'), 1.44-1.59 (2H, m, 2 x H3'), 1.78 (2H, app quin, *J* 7.5 Hz, 2 x H3), 2.26 (2H, app tt, *J* 7.5 and 1.5 Hz, 2 x H4), 2.35 (2H, t, *J* 8.0 Hz, 2 x H4'), 3.72 (2H, tt, *J* 7.5 Hz, 1.5 Hz, 2 x H2); $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 13.9, 22.6, 22.7, 28.6, 33.5, 37.1, 60.7, 178.6; *m/z* (EI) 126.0114 ($M-H^+$ requires 126.0115) 126 (100%)

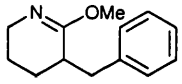
## 3,4,5,6-tetrahydro-2-methoxy-3-methylpyridine 224




224

Reaction of **15** (0.2255 g, 1.98 mmol) in THF (8 ml) with a 1.7M solution of $^t$butyl lithium in hexanes (1.7 ml, 2.97 mmol) and methyl iodide (0.19 ml, 2.97 mmol) according to general procedure B afforded the title compound **224** as a clear oil (0.1595 g, 1.25 mmol) in 63% yield, $\nu_{max}/cm^{-1}$1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.09 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.30-1.64 (3H, bm, 2 x H3 and 1 x H4), 1.73-1.85 (1H, bm, 1 x H4), 2.24 (1H, app hex, *J* 7.0 Hz, 1 x H5), 3.39 (2H, dt, *J* 5.8 and 1.2 Hz, 2 x H2), 3.53 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 18.9, 29.4, 29.8, 31.8, 47.9, 52.6, 166.5; *m/z* (EI) 128.1068 ($M-H^+$ requires 128.1070) 128 (100%)

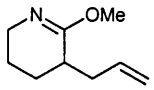
## 3-benzyl-3,4,5,6-tetrahydro-2-methoxypyridine 217




217

Reaction of **15** (0.2190 g, 1.92 mmol) in THF (8 ml) with a 1.7M solution of $^t$butyl lithium in hexanes (1.7 ml, 2.89 mmol) and benzyl bromide (0.34 ml, 2.88 mmol) according to general procedure B afforded the title compound **217** as a clear oil (0.3396 g, 1.67 mmol) in 87% yield, $\nu_{max}/cm^{-1}$1674 (C=N): $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.33-1.60 (4H, bm, 2 x H3 and 2 x H4), 2.38-2.49 (1H, bm, 1 x H5), 2.55 (1H, dd, *J* 13.2 and 3.2 Hz, 1 x H1'), 3.12 (1H, dd, *J* 13.2 and 3.6 Hz, 1 x H1'), 3.41-3.34 (2H, bm, 2 x H2), 3.61 (3H, s, OMe), 7.07-7.25 (5H, bm, $H_{Ar}$); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 21.1, 25.4, 38.3, 38.3, 47.7, 52.4, 126.5, 128.7, 129.6, 140.2, 164.7, *m/z* (EI) 204.1385 ($M-H^+$ requires 204.1383) 204 (100%)

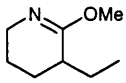
## 3-allyl-3,4,5,6-tetrahydro-2-methoxypyridine 225




225

Reaction of **15** (0.2500 g, 2.20 mmol) in THF (5 ml) with a 1.7M solution of $^{t}$butyl lithium in hexanes (2.0 ml, 3.30 mmol) and allyl bromide (0.57 ml, 6.60 mmol) according to general procedure B afforded the title compound **225** as a clear oil (0.2223 g, 1.45 mmol) in 66% yield, $\nu_{max}/cm^{-1}$ 1641 (C=C), 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.31-1.77 (4H, bm, 2 x H3 and 2 x H4), 2.08-2.29 (2H, bm, 2 x H3'), 2.34-2.44 (1H, m, 1 x H5), 3.37 (2H, app q, *J* 5.6 Hz, 2 x H2), 3.53 (3H, s, OMe), 4.96 (1H, dm, *J* 10.0 Hz, 1 x H1'$^{cis}$), 4.98 (1H, dm, *J* 17.0 Hz, 1 x H1'$^{trans}$), 5.65 (1H, ddt, *J* 6.8, 10.0 and 17.0 Hz, 1 x H2'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 21.4, 25.8, 36.2, 36.7, 47.4, 52.3, 117.1, 136.5, 164.7; *m/z* (EI) 154.1226 (M-H$^+$ requires 154.1228) 154 (100 %).

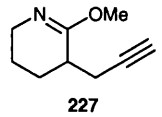
## 3-ethyl-3,4,5,6-tetrahydro-2-methoxypyridine 226




226

Reaction of **15** (0.2255 g, 1.98 mmol) in THF (7 ml) with a 1.7M solution of $^{t}$butyl lithium in hexanes (1.7 ml, 2.97 mmol) and ethyl bromide (0.44 ml, 5.92 mmol) according to general procedure B afforded the title compound **226** as a clear oil (0.1595 g, 1.25 mmol) in 68% yield; $\nu_{max}/cm^{-1}$ 1675 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.83 (3H, t, *J* 7.5 Hz, 3 x H1'), 1.31-1.79 (6H, bm, 2 x H3, 2 x H4 and 2 x H2'), 2.04-2.15 (1H, m, 1 x H5), 3.33-3.43 (2H, m, 2 x H2), 3.53 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 11.6, 21.6, 25.3, 25.8, 38.0, 47.5, 52.3, 165.6; *m/z* (EI) 142.1226 (M-H$^+$ requires 142.1226) 142 (59%), 128 (M-H$^+$ - OMe + $NH_3$, 100) 142 (62).

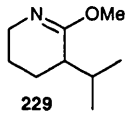
## 3,4,5,6-tetrahydro-2-methoxy-3-(prop-2-ynyl)pyridine 227




227

Reaction of **15** (0.2337 g, 2.05 mmol) in THF (6 ml) with a 1.7M solution of $^{t}$butyl lithium in hexanes (1.55 ml, 3.08 mmol) and propargyl bromide (80% in toluene) (0.55 ml, 6.16 mmol) according to general procedure B afforded the title compound **227** as a clear oil (0.2407 g, 1.59 mmol) in 78% yield, $\nu_{max}/cm^{-1}$ 1678 (C=N), 2118 (C≡C), 3296 (C≡C-H); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.39-1.55 (1H, bm, 1 x H4), 1.56-1.76 (2H, bm, 1 x H3 and 1 x H4), 1.83-1.90 (1H, m, 1 x H3), 1.92 (1H, t, *J* 2.6 Hz, 1 x H1'), 2.34 (2H, m, 1 x H3' and 1 x H5), 2.52 (1H, app ddd, *J* 2.6, 7.35 and 12.6 Hz, 1 x H3'), 3.36-3.45 (2H, m, 2 x H2), 3.54, (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 21.7, 22.0, 26.2, 35.9, 47.4, 52.5, 70.2, 82.1, 163.2; *m/z* (EI) 152.1070 ($M\text{-}H^+$ requires 152.1070) 152 (100%), 138 ($M\text{-}H^+$ - OMe + $NH_3$, 17).

## 3,4,5,6-tetrahydro-3-isopropyl-2-methoxypyridine 229

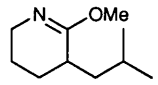



229

Reaction of **15** (0.2620 g, 2.30 mmol) in THF (5 ml) with a 1.7M solution of $^{n}$butyl lithium in hexanes (1.4 ml, 3.45 mmol) and $^{i}$propyl iodide (0.79 ml, 7.90 mmol) according to general procedure B afforded the title compound **229** as a clear oil (0.2952 g, 1.90 mmol) in 83% yield, $\nu_{max}/cm^{-1}$ 1675 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.74 (3H, d, *J* 7.0 Hz, 3 x H1'), 0.84 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.34-1.44 (2H, bm, 2 x H4), 1.55-1.71 (2H, bm, 2 x H3), 2.13-2.24 (1H, bm, 1 x H5), 2.22 (1H, m, 1 x H2'), 3.17-3.30 (2H, bm, 2 x H2), 3.53 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 18.0, 20.2, 21.6, 22.9, 28.9, 42.6, 44.3, 52.3.[7] *m/z* (EI) 156.0592 ($M\text{-}H^+$ requires 156.0591) 156 (100%)

[7] No quaternary peak owing to a weak signal

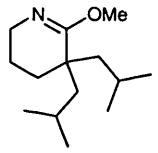
## 3,4,5,6-tetrahydro-3-isobutyl-2-methoxypyridine 228




228

Reaction of **15** (0.2060 g, 1.81 mmol) in THF (5 ml) with a 1.7M solution of $^{n}$butyl lithium in hexanes (1.1 ml, 2.72 mmol) and $^{i}$butyl bromide (0.62 ml, 5.44 mmol) according to general procedure B afforded the title compound **228** as a clear oil (0.1963 g, 1.16 mmol) in 64% yield, $\nu_{max}/cm^{-1}$ 1675 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.81 (3H, d, *J* 6.4 Hz, 3 x H1'), 0.84 (3H, d, *J* 6.4 Hz, 3 x H1'), 1.13-1.27 (2H, m, 2 x H3'), 1.34-1.77 (5H, bm, 2 x H3, 2 x H4 and 1 x H2'), 2.13-2.24 (1H, m, 1 x H5), 3.38 (2H, dt, *J* 1.2 and 5.6 Hz, 2 x H2), 3.52 (3H, s, OMe), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 20.8, 21.3, 23.6, 25.1, 25.9, 34.1, 41.3, 46.3, 51.9, 165.8; *m/z* (EI) 170.0758 ($M\text{-}H^+$ requires 170.0757) 170 (100%).

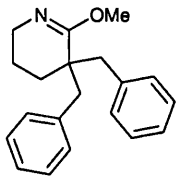
## 3,4,5,6-tetrahydro-3,3-diisobutyl-2-methoxypyridine 230




230

Reaction of **160** (0.1203 g, 0.71 mmol) in THF (5 ml) with a 1.7M solution of $^{n}$butyl lithium in hexanes (0.63 ml, 1.06 mmol), potassium $^{t}$butoxide (0.0921 g, 0.75 mmol) and $^{i}$butyl bromide (0.24 ml, 2.12 mmol) according to general procedure B afforded the title compound **230** as a clear oil (0.1087 g, 0.48 mmol) in 64% yield, $\nu_{max}/cm^{-1}$ 1675 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.77 (6H, d, *J* 6.4 Hz, 3 x H1'), 0.82 (6H, d, *J* 6.4 Hz, 3 x H1'), 1.17 (4H, dd, *J* 4.0 and 13.6 Hz, 4 x H3'), 1.47-1.66 (6H, bm, 2 x H3, 2 x H4, 2 x H2'), 3.41 (2H, t, *J* 5.65 Hz, 2 x H2), 3.48 (3H, s, OMe); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 21.6, 23.7, 24.9, 26.1, 30.9, 41.4, 47.9, 49.6, 51.7, 167.9; *m/z* (EI) 226.2165 ($M\text{-}H^+$ requires 226.2165) 226 (100%).

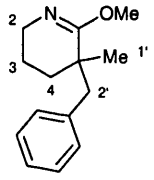
## 3,3-dibenzyl-3,4,5,6-tetrahydro-2-methoxypyridine 231



231

Reaction of **217** (0.0988 g, 0.49 mmol) in THF (5 ml) with a 1.5M solution of $^{n}$butyl lithium in hexanes (0.49 ml, 0.73 mmol), potassium $^{t}$butoxide (0.0862 g, 0.768 mmol) and benzyl bromide (0.087 ml, 0.73 mmol) according to general procedure C afforded the title compound **231** as a clear oil (0.1251 g, 0.43 mmol) in 87% yield, $\nu_{max}/cm^{-1}$ 1675 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.32-1.42 (2H, m, 2 x H4), 1.48-1.55 (2H, m, 2 x H3), 2.46 (2H, d, *J* 13.2 Hz, 2 x H1'), 2.87 (2H, t, *J* 5.7 Hz, 2 x H2), 3.20 (2H, d, *J* 13.2 Hz, 2 x H1'), 3.65 (3H, s, OMe), 6.86-7.29 (10H, bm, 10 x $H_{AR}$); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 19.0, 27.4, 32.5, 36.9, 44.2, 50.6, 125.3, 127.3, 128.0, 129.3, 163.6; *m/z* (EI) 294.2145 ($M\text{-}H^+$ requires 294.2146) 294 (100%).

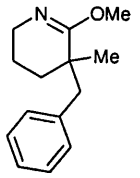
## 3-benzyl-3,4,5,6-tetrahydro-2-methoxy-3-methylpyridine 232



232

Reaction of **224** (0.1212 g, 0.95 mmol) in THF (5 ml) with a 1.5M solution of $^{n}$butyl lithium in hexanes (1.0 ml, 1.48 mmol), potassium $^{t}$butoxide (0.1785, 1.46 mmol) and benzyl bromide (1.7 ml, 1.43 mmol) according to general procedure C afforded the title compound **232** as a clear oil (0.1486 g, 0.68 mmol) in 72% yield, $\nu_{max}/cm^{-1}$ 1675 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.15 (3H, s, 3 x H1'), 1.35-1.56 (4H, bm, 2 x H3, 2 x H4), 2.51 (d, *J* 13.2 Hz, 1 x H2'), 2.81 (2H, t, *J* 5.7 Hz, 2 x H2), 3.15 (1H, d, *J* 13.2 Hz, 1 x H2'), 3.64 (3H, s, OMe), 6.95-7.25 (5H, bm, 5 x $H_{Ar}$); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 19.7, 26.4, 28.1, 31.2, 37.2, 45.4, 51.0, 123.2, 127.8, 128.1, 129.8, 164.9; *m/z* (EI) 218.1186 ($M\text{-}H^+$ requires 218.1186) 218 (100%).

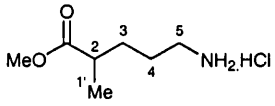
## 3-benzyl-3,4,5,6-tetrahydro-2-methoxy-3-methylpyridine 232




232

Reaction of **217** (0.1298 g, 0.64 mmol) in THF (5 ml) with a 1.5M solution of $^{n}$butyl lithium in hexanes (0.64 ml, 0.96 mmol), potassium $^{t}$butoxide (0.1182 g, 0.96 mmol) and methyl iodide (0.060 ml, 0.96 mmol) according to general procedure C afforded the title compound **232** as a clear oil (0.0974 g, 0.45 mmol) in 70% yield.

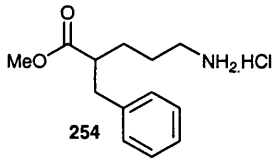
## 2-Methyl-pentanoic acid methyl ester 253




253

Reaction of **224** (0.0351 g, 0.276 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (4.1 ml, 0.414 mmol) according to general procedure E afforded the title compound **253** (0.0460 g, 0.254 mmol) as a semi crystalline material in 92% yield, $\nu_{max}/cm^{-1}$ 3441 (NH), 1643 (C=O); $\delta_H$(300MHz, MeOD) 1.07 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.30-1.68 (4H, bm, 2 x H3, 2 x H4), 2.41 (1H, app hept, *J* 7.0 Hz, 1 x H2), 2.80 (2H, t, *J* 6.8 Hz, 2 x H5), 3.56 (3H, s, OMe), $\delta_C$(75MHz, MeOD) 17.9, 26.7, 31.8, 40.5, 41.0, 52.6, 178.6, *m/z* (EI) 146.1172 (M-$H^+$ requires 146.1176) 146 (100%).

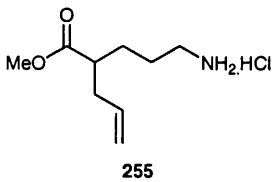
## Methyl 5-amino-2-benzylpentanoate hydrochloride 253




254

Reaction of **217** (0.0254 g, 0.125 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (1.9 ml, 0.186 mmol) according to general procedure E afforded the title compound **253** (0.0305 g, 0.119 mmol) as a semi crystalline material in 95% yield, $\nu_{max}/cm^{-1}$ 3428 (NH), 1642 (C=O), $\delta_H$(300MHz, MeOD) 1.46-1.64 (4H, bm, 2 x H3, 2 x H4), 2.58-2.87 (5H, bm, 2 x H1', 1 x H2, 2 x H5), 3.48 (3H, s, OMe), 7.02-7.21 (5H, bm, 5 x $H_{Ar}$); $\delta_C$(75MHz, MeOD) 26.8, 30.3, 39.9, 41.0, 48.9, 52.6, 128.0, 129.9, 130.7, 140.7, 177.5.[8]

## Methyl 2-(3-aminopropyl)pent-4-enoate hydrochloride 255

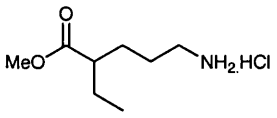



255

Reaction of **225** (0.0289 g, 0.189 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (2.8 ml, 0.283 mmol) according to general procedure E afforded the title compound **255** (0.0351 g, 0.170 mmol) as a semi crystalline material in 90% yield, $\nu_{max}/cm^{-1}$ 1660 (C=O); $\delta_H$(300MHz, MeOD) 1.54-1.74 (4H, bm, 2 x H3, 2 x H4), 2.26 (1H, dd, *J* 7.3, 14.1 Hz, 1 x H3'), 2.38 (1H, dd, *J* 7.3, 14.1 Hz, 1 x H3'), 2.47-2.58 (1H, bm, 1 x H2), 2.93 (2H, td, *J* 7.3, 2.5 Hz, 2 x H5), 3.67, (3H, s, OMe), 5.02 (1H, ddd, *J* 10.7, 1.0, 1.0 Hz, 1 x $H1'^{cis}$), 5.06 (1H, ddt, *J* 17.0, 1.7, 1.3 Hz, 1 x $H1'^{cis}$), 5.76 (1H, ddt, *J* 17.0, 10.7, 7.0 Hz, 1 x H2'); $\delta_C$(75MHz, MeOD) 26.8, 29.9, 37.9, 41.0, 46.4, 52.6, 117.9, 136.8, 177.5.[viii]

[8] Mass spectrum matched that of the corresponding lactam.

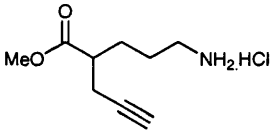
## Methyl 5-amino-2-ethylpentanoate hydrochloride 256




256

Reaction of **226** (0.0151 g, 0.107 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (1.6 ml, 0.160 mmol) according to general procedure E afforded the title compound **256** (0.0169 g, 0.087 mmol) as a semi crystalline material in 81% yield, $\nu_{max}/cm^{-1}$ 1632 (C=O); $\delta_H$(300MHz, MeOD) 0.81 (3H, t, *J* 7.0 Hz , 3 x H1'), 1.41-1.64 (6H, 2 x H2', 2 x H3, 2 x H4), 2.19-2.33 (1H, bm, 1 x H2), 2.83 (2H, t, *J* 6.0 Hz, 2 x H5), 3.60 (3H, s, OMe); $\delta_C$(75MHz, MeOD) 12.8, 26.9, 26.9, 29.9, 41.1, 48.3, 52.5, 178.2, *m/z* (EI) 131 (-Et 16), 127 (amide 32) 87 (-$CO_2$Me 100%).

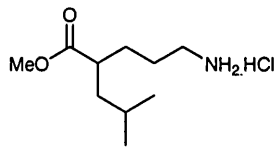
## Methyl 2-(3-aminopropyl)pent-4-ynoate hydrochloride 257




257

Reaction of **227** (0.0270 g, 0.179 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (2.3 ml, 0.230 mmol) according to general procedure E afforded the title compound **257** (0.0357 g, 0.173 mmol) as a semi crystalline material in 97% yield, $\nu_{max}/cm^{-1}$ 1634 (C=O), $\delta_H$(300MHz, MeOD) 1.47-1.70 (4H, bm, 2 x H3, 2 x H4), 2.24 (1H, t, *J* 2.6 Hz, 1 x H1'), 2.31-2.41 (2H, bm, 2 x H3'), 2.52 (1H, app quin, *J* 7.0 Hz, 1 x H2), 2.81 (2H, t, *J* 7.5 Hz, 2 x H5), 3.60 (3H, s, OMe); $\delta_C$(75MHz, MeOD, $Me_4Si$) 22.4, 26.6, 29.8, 41.0, 45.6, 52.9, 72.0, 82.0, 176.5.[viii]

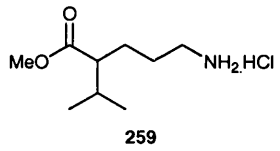
## Methyl 2-(3-aminopropyl)-4-methylpentanoate hydrochloride 258




258

Reaction of **228** (0.0301 g, 0.178 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (2.7 ml, 0.267 mmol) according to general procedure E afforded the title compound **258** (0.0361 g, 0.162 mmol) as a semi crystalline material in 91% yield, $\nu_{max}/cm^{-1}$ 1719 (C=O), $\delta_H$(300MHz, MeOD) 0.81 (6H, app t, *J* 6.6 Hz, 6 x H1'), 1.11-1.19 (1H, bm, 1 x H2'), 1.35-1.62 (6H, bm, 2 x H3, 2 x H4, 2 x H3'), 2.41 (1H, app hept, *J* 4.5 Hz, 1 x H2), 2.76-2.85 (2H, bm, 2 x H5), 3.59 (3H, s, OMe); $\delta_C$(75MHz, MeOD) 22.8, 24.5, 27.0, 27.8, 31.1, 41.0, 43.4, 45.0, 52.5, 178.5.

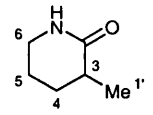
## Methyl 5-amino-2-isopropylpentanoate hydrochloride 259




259

Reaction of **229** (0.0189 g, 0.122 mmol) in $D_2O$ (0.7 ml) acidified with conc. HCl (0.0191 g, 0.189 mmol) over 10 hours afforded the title compound **259** in a quantitative yield as a $D_2O$ solution, removal of the solvent *in vacuo* afforded the title compound as a semi crystalline compound (0.0254 g, 0.0121 mol) in 92% yield; $\delta_H$(300MHz, $D_2O$) 0.57 (3H, d, *J* 7.0 Hz, 3 x H1'), 0.69 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.33-1.56 (2H, bm, 2 x H4), 1.62-1.80 (2H, bm, 2 x H3), 2.12 (1H, m, 1 x H2'), 2.47-2.56 (1H, m, 1 x H2), 3.18-3.39 (2H, bm, 2 x H5), 3.81 (3H, s, OMe); $\delta_C$(75MHz, $D_2O$) 17.3, 19.1, 19.3, 19.6, 28.7, 43.5, 44.0, 58.1, 178.5.[viii]

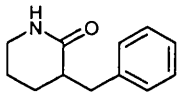
## 3-methylpiperidin-2-one 262[111]




262

Reaction of **253** (0.0112 g, 0.062 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0085 g, 0.066 mol) for 24 hours afforded the title compound **262** as a methanol:water solution (0.0063 g, 0.056 mmol) in 91% yield; $\nu_{max}/cm^{-1}$ 1665 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.11 (3H, d, *J* 7.1 Hz, 3 x H1'), 1.43 (1H, dddd, *J* 3.2, 8.5, 9.8 and 13.0 Hz, 1 x H4), 1.55-1.83 (2H, bm, 2 x H5), 1.89 (1H, app dtd, *J* 13.2, 6.8, 3.2 Hz, 1 x H4), 2.27 (1H, app hept, *J* 7.1 Hz, 1 x H3), 3.19 (3H, t, *J* 5.5 Hz, 2 x H6), 5.81 (1H, bs, N*H*); $\delta_C$(75MHz, MeOD) 18.5, 22.1, 30.3, 37.5, 48.8, 179.3.

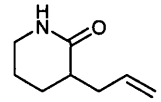
## 3-benzylpiperidin-2-one 263[111]




263

Reaction of **254** (0.0154 g, 0.059 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0111 g, 0.087 mol) for 24 hours afforded the title compound **263** as a methanol:water solution (0.0108 g, 0.057 mmol) in 97% yield; $\nu_{max}/cm^{-1}$ 1642 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.32-1.46 (1H, bm, 1 x H4), 1.51-1.81 (3H, bm, 2 x H5, 1 x H4), 2.48 (1H, tdd, *J* 10.0, 5.5, 3.8 Hz, 1 x H3), 2.61 (1H, dd, *J* 10.0, 13.4 Hz, 1 x H1'), 3.17-3.25 (2H, m, 2 x H6), 3.34 (1H, dd, *J* 13.4, 3.6 Hz, 1 x H1'), 5.76 (1H, bs, N*H*), 7.10-7.27 (5H, bm, $H_{Ar}$); $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 18.5, 22.1, 30.3, 37.5, 48.8, 127.9, 130.0, 130.8, 141.3, 179.3; *m/z* (EI) 190.1226 ($M\text{-}H^+$ requires 190.1229) 190 (100%).

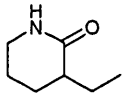
## 3-allylpiperidin-2-one 264[185]



264

Reaction of **255** (0.0127 g, 0.061 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0121 g, 0.095 mol) for 24 hours afforded the title compound **264** as a methanol:water solution (0.0079 g, 0.057 mmol) in 94% yield; $\nu_{max}/cm^{-1}$ 1661 (C=O), 1637 (C=C); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.36-1.55 (1H, bm, 1 x H4), 1.58-1.92 (3H, bm, 2 x H5, 1 x H4), 2.15-2.35 (2H, bm, 1 x H3, 1 x H3'), 2.56-2.65 (1H, m 1 x H3'), 3.20-3.26 (2H, m, 2 x H6), 4.98 (1H, dm, *J* 10.0 Hz, 1 x H1'$^{cis}$), 5.01 (1H, dm, *J* 17.0 Hz, 1 x H1'$^{trans}$), 5.71 (1H, tdd, *J* 17.0, 10.0, 7.0 Hz, 1 x H2'), 5.80 (1H, bs, N*H*); $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 21.8, 26.1, 36.3, 41.0, 43.0, 117.3, 136.2, 171.5; *m/z* (EI) 152.1305 ($M\text{-}H^+$ requires 152.1074) 152 (100%).

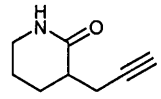
## 3-ethylpiperidin-2-one 265[185]



265

Reaction of **257** (0.0051 g, 0.026 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0045 g, 0.035 mol) for 24 hours afforded the title compound **265** as a methanol:water solution (0.0027 g, 0.021 mmol) in 82% yield; $\nu_{max}/cm^{-1}$ 1670 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.82 (3H, t, *J* 7.4 Hz, 3 x H1'), 1.38-1.87 (6H, bm, 2 x H5, 2 x H4, 2 x H2'), 2.04-2.16 (1H, bm, 1 x H3), 3.11-3.19 (2H, bm, 2 x H6), 5.91 (1H, bs, N*H*); $\delta_C$(75MHz, MeOD) 12.4, 22.3, 26.0, 26.6, 43.5, 43.7, 178.6; *m/z* (EI) 128.1075 ($M\text{-}H^+$ requires 128.1076) 128 (100%).

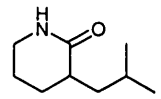
## 3-(prop-2-ynyl)piperidin-2-one 266



266

Reaction of **258** (0.0168 g, 0.082 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0122 g, 0.095 mol) for 24 hours afforded the title compound **266** as a methanol:water solution (0.0104 g, 0.076 mmol) in 93% yield; $\nu_{max}/cm^{-1}$ 1658 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.64-1.92 (4H, bm, 2 x H5, 2 x H4), 1.93 (1H, t, *J* 2.5 Hz, 1 x H1'), 2.33-2.43 (1H, m, 1 x H3), 2.44-2.50 (1H, m, 1 x H3'), 2.64-2.72 (1H, m, 1 x H3'), 3.23-3.29 (2H, m, 2 x H6), 5.89 (1H, bs, N*H*); $\delta_C$(75MHz, MeOD) 22.1, 22.6, 27.3, 41.5, 43.7, 72.1, 83.2, 176.2.

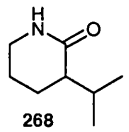
## 3-isobutylpiperidin-2-one 267[139]



267

Reaction of **259** (0.0997 g, 0.045 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0084 g, 0.066 mol) for 24 hours afforded the title compound **267** as a methanol:water solution (0.0065 g, 0.042 mmol) in 93% yield; $\nu_{max}/cm^{-1}$ 1636 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.79 (3H, d, *J* 6.2 Hz, 3 x H1'), 0.83 (3H, d, *J* 6.2 Hz, 3 x H1'), 1.14-1.30 (2H, bm, 2 x H3'), 1.33-1.52 (1H, bm, 1 x H2'), 1.52-1.67 (2H, bm, 2 x H4), 1.69-1.91 (2H, bm, 2 x H5), 2.13-2.26 (1H, m, 1 x H3), 3.13-3.22 (2H, m, 2 x H6), 5.79 (1H, bs, N*H*); $\delta_C$(75MHz, MeOD) 18.5, 21.0, 22.1, 22.8, 24.1, 30.3, 37.5, 43.2, 179.3.

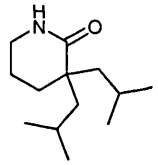
## 3-isopropylpiperidin-2-one 268



268

Reaction of **260** (0.0038 g, 0.018 mmol) in MeOH (0.6 ml) and $D_2O$ (0.1 ml) with potassium carbonate (0.0041 g, 0.032 mol) for 24 hours afforded the title compound **268** as a methanol:water solution (0.0023 g, 0.016 mmol) in 90% yield; $\nu_{max}/cm^{-1}$ 1632 (C=O); $\delta_H$(300MHz, MeOD) 0.73 (3H, d, *J* 7.0 Hz, 3 x H1'), 0.86 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.13-1.29 (1H, m, 1 x H2'), 1.36-1.63 (2H, bm, 2 x H5), 1.67-1.87 (2H, m, 2 x H4), 2.30 (1H, app hexd, *J* 7.0 and 3.0 Hz, 1 x H3), 3.03-3.19 (2H, m, 2 x H6); $\delta_C$(75MHz, MeOD) 18.4, 21.1, 22.0, 23.2, 29.8, 43.6, 48.0, no carbonyl peak observed

## 3,3-diisobutylpiperidin-2-one 261

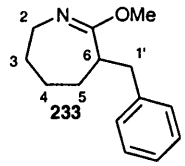


261

Reaction of **230** (0.0076 g, 0.034 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (0.7 ml, 0.051 mmol) solution according to general procedure E afforded **261** as a solid (0.0070 g, 0.033 mmol) in 98% yield; $\nu_{max}/cm^{-1}$ 1639 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.80 (6H, d, *J* 6.6 Hz, 6 x H1'), 0.83 (6H, d, *J* 6.6 Hz, 6 x H1'), 1.20 (2H, d, *J* 4.0 Hz, 2 x H3'), 1.25 (2H, d, *J* 4.0 Hz, 2 x H3'), 1.52-1.74 (8H, bm, 2 x H5, 2 x H4, 2 x H2', 2 x H3'), 3.16-3.23 (2H, m, 2 x H6), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 20.4, 24.4, 24.9, 25.8, 29.3, 43.3, 48.1.[9]

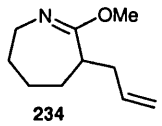
[9] Neither quaternary peaks observed on account of weak signal.

## 6-benzyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine 233




Reaction of **16** (0.2279 g, 1.79 mol) in THF (10 ml) with a 1.7M solution of $^{t}$BuLi in hexanes (1.6 ml, 1.6 ml, 2.70 mmol) and potassium $^{t}$butoxide (0.3324 g, 2.72 mol) according to general procedure C afforded the title compound **233** as a clear oil (0.3034 g, 1.40 mmol) in 78%; $\nu_{max}/cm^{-1}$ 1668 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.16-1.71 (5H, bm, 2 x H3, 2 x H4, 1 x H5), 1.74-1.86 (1H, bm, 1 x H5), 2.56 (1H, dd, *J* 8.9, 13.8 Hz, 1 x H1'), 2.80 (1H, ddd, *J* 2.2, 9.0, 8.9 Hz, 1 x H6), 3.05 (1H, dd, *J* 6.4, 13.8 Hz, 1 x H1'), 3.33 (2H, ddd, *J* 1.7, 9.0, 13.2 Hz, 2 x H2), 3.50 (3H, s, OMe), 7.08-7.24 (5H, bm, $H_{Ar}$), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 27.8, 28.6, 29.1, 37.1, 44.5, 47.7, 52.9, 126.4, 128.7, 129.3, 140.9, 169.6; *m/z* (EI) 218.1540 ($M\text{-}H^+$ requires 218.1539) 218 (100%), 204 ($M\text{-}H^+$ - OMe + $NH_3$, 4)

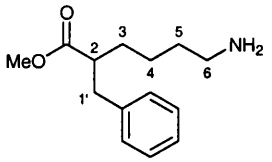
## 6-allyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine 234




Reaction of **16** (0.5756 g, 4.553 mmol) in THF (20 ml) with a 2.4M solution of $^{t}$butyl lithium in hexanes (3.7 ml, 6.79 mmol), potassium $^{t}$butoxide (0.83 g, 6.79 mmol) and allyl bromide (1.18 ml, 13.58 mol) according to general procedure C afforded the title compound **234** (0.5450 g, 3.26 mmol) in 74% yield as a clear oil; $\nu_{max}/cm^{-1}$ 1668 (C=N), 1652 (C=C); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.17-1.44 (2H, bm, 2 x H4), 1.51-1.67 (2H, bm, 2 x H5), 1.75-1.89 (2H, bm, 2 x H3), 2.06 (1H, ttd, *J* 15.6, 7.7 and 0.8 Hz, 1 x H3'), 2.43 (1H, ttd, 14.0, 6.2, 1.5, 1 x Hz, 1 x H3'), 2.61 (1H, ddt, *J* 2.3, 9.6, 7.0 Hz, 1 x H6), 3.25-3.35 (2H, bm, 2 x H2), 3.52 (3H, s, OMe), 4.94 (1H, ddt, *J* 1.1, 1.1, 10.0 Hz, 1 x H1'$^{cis}$), 4.97 (1H, ddt, *J* 1.5, 1.8, 17.1 Hz, 1 x H1'$^{trans}$), 5.74 (1H, dddd *J* 7.0, 10.0, 16.2, 17.1 Hz, 1 x H2'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 37.7, 29.1, 29.2, 35.6,

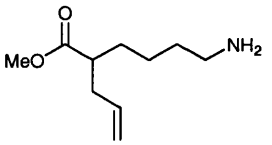
42.4, 47.7, 52.7, 116.6, 137.4, 169.8; *m/z* (EI) 168.1099 ($M-H^+$ requires 168.1101) 168 (100%)

## Methyl 6-amino-2-benzylhexanoate 362



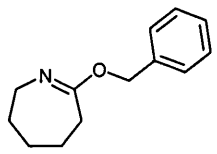

Reaction of **233** (0.0268 g, 0.123 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (1.6 ml, 0.160 mmol) according to general procedure E afforded the title compound **362** (0.0257 g, 0.109 mmol) as a pale yellow oil in 89% yield; $\nu_{max}/cm^{-1}$ 1738 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.12-2.01 (6H, bm, 2 x H3, 2 x H4, 2 x H5), 2.44-3.33 (5H, bm, 2 x H1', 1 x H2, 2 x H6), 3.51 (3H, s, OMe), 7.02-7.28 (5H, bm, $H_{Ar}$); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 28.9, 29.3, 30.0, 37.4, 42.9, 45.5, 52.0, 126.5, 128.8, 129.2, 140.5, 180.7; *m/z* (EI) 236.2111 ($M-H^+$ requires 236.2112) 236 (100%).

## Methyl 2-allyl-6-aminohexanoate 363




Reaction of **234** (0.0241 g, 0.144 mmol) in $CHCl_3$ (0.5 ml) with 0.1M HCl (1.6 ml, 0.160 mmol) according to general procedure E afforded the title compound **363** (0.0232 g, 0.125 mmol) as a clear oil in 87% yield; $\nu_{max}/cm^{-1}$ 1725 (C=O), 1642 (C=C); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.27 (2H, app q, *J* 7.5 Hz, 2 x H4), 1.34-1.73 (4H, bm, 2 x H3, 2 x H5), 2.10-2.49 (3H, bm, 1 x H2, 2 x H3'), 2.71 (2H, t, *J* 7.1 Hz, 2 x H6), 3.60 (3H, s, OMe), 4.94 (1H, dm, *J* 10.0 Hz, 1 x $H1'^{cis}$), 4.98 (1H, dm, *J* 17.0 Hz, 1 x $H1'^{trans}$), 5.65 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, 1 x H2'); $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 24.9, 31.3, 31.7, 36.8, 41.1, 45.6, 51.9, 117.2, 135.7, 176.4, *m/z* (EI) 226.2165 ($M-H^+$ requires 226.2165) 226 (100%).

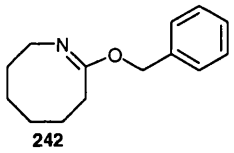
## 7-(benzyloxy)-3,4,5,6-tetrahydro-2H-azepine 241



241

Trifluoroacetic acid (0.38 ml, 5.00 mmol) was added to a gently stirred solution of **16** (0.5781 g, 4.55 mmol) in toluene (20 ml) in the presence of 5Å molecular sieves, and the reaction mixture allowed to stir for 16 hours. The reaction was quenched using dilute potassium carbonate (0.9626 g, 7.52 mmol) solution (50 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound **241** (0.6917 g, 3.05 mmol) in 67% yield as a clear oil; $\nu_{max}/cm^{-1}$ 1677 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.44-1.59 (4H, bm, 2 x H4, 2 x H5), 1.67-1.77 (2H, bm, 2 x H3), 2.41 (2H, m, 2 x H6), 3.39 (2H, m, 2 x H2), 4.93 (2H, s, $OCH_2$), 7.19-7.33 (5H, m, $H_{Ar}$), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 23.9, 28.4, 31.7, 32.7, 49.2, 67.3, 128.0, 128.2, 128.8, 137.9, 169.6, *m/z* (EI) 204.1384 ($M\text{-}H^+$ requires 204.1383) 204 (100%).

## 2-(benzyloxy)-3,4,5,6,7,8-hexahydroazocine 242

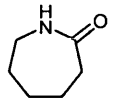


242

Trifluoroacetic acid (0.37 ml, 4.81 mmol) was added to a gently stirred solution of **237** (0.6111 g, 4.36 mmol) on toluene (20 ml) in the presence of 5Å molecular sieves, and the reaction mixture allowed to stir for 16 hours. The reaction was quenched using dilute potassium (0.9025 g, 7.05 mmol) carbonate solution (50 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound **242** (0.3885

g, 1.79 mmol) in 41% yield as a clear oil; $\nu_{max}/cm^{-1}$ 1679 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.33-1.71 (8H, bm, 2 x H3, 2 x H4, 2 x H5, 2 x H6), 2.37 (2H, t, *J* 6.3 Hz, 2 x H7), 3.36 (2H, t, *J* 5.8 Hz, 2 x H2), 4.84 (2H, s, $OCH_2$), 7.10-7.36 (5H, bm, 5 x $H_{Ar}$); $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 24.9, 26.4, 28.0, 28.5, 31.5, 49.8, 67.8, 128.0, 128.3, 129.0, 138.0, 170.1; *m/z* (EI) 218.1540 ($M-H^+$ requires 218.1541) 218 (100%).

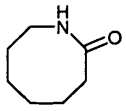
## Caprolactam 10



10

Benzyl capro lactim ether **241** (0.0297 g, 0.146 mmol) was treated with $Pd(OH)_2$ (0.0153 g, 0.028 mmol) as described in general procedure F to afford the title compound **10** (0.0158 g, 0.140 mmol) in 96% yield. Spectroscopic data matched that of an authentic sample of caprolactam.

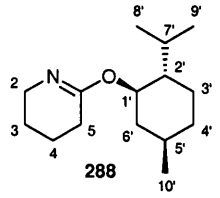
## Oenantholactam 243



243

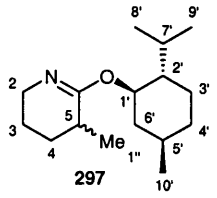
Benzyl oenantholactim ether **242** (0.0197 g, 0.091 mmol) was treated with $Pd(OH)_2$ (0.0095 g, 0.015 mmol) as described in general procedure F to afford the title compound **243** (0.0112 g, 0.088 mmol) in 97% yield. Spectroscopic data matched that of an authentic sample of oenantholactam.

## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3,4,5,6-tetrahydropyridine 288




A solution of **15** (6.36 g, 56.3 mmol) and (-)-menthol (11.44 g, 73.2 mmol) in toluene (50 ml) was allowed to stand in the presence of 5Å molecular sieves (9.6 g) for 30 minutes. Trifluoroacetic acid (5.5 ml, 73.2 mmol) was added to the solution and allowed to stir for 18 hours. 1M potassium carbonate solution (12.8 g, 100 mmol) was added to the reaction mixture and the reaction was extracted with $Et_2O$ (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product, which was purified by silica gel chromatography (3% EtOAc/petrol) to afford the title compound **288** as a crystalline white solid (5.65 g, 27.4 mmol) in 48% yield, $[\alpha]_D^{25}$ –96.4 (*c* 0.79, EtOAc); $\nu_{max}/cm^{-1}$ 1674 (C=N); mp = 37-38 °C; $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.69-0.82 (11H, bm), 0.98 (1H, m), 1.26-1.71 (8H, bm), 1.86 (1H, m, 1 x H7'), 2.05 (3H, m, 2 x H5, 1 x H6'), 3.90 (2H, ttt, *J* 7.1, 5.7, 1.1 Hz, 2 x H2), 4.62 (1H, td, *J* 10.9, 4.3 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.2, 20.9, 21.3, 22.6, 23.0, 24.1, 26.8, 26.8, 31.6, 35.0, 40.2, 47.2, 48.1, 72.8, 162.01, *m/z* (CI) 238.2168 ($M\text{-}H^+$ requires 236.2165) 238 (100%); *m/z* (EI) 222 ($M^+$-Me, 1%), 194 ($M^+$-$C_3H_7$, 6%), 100 ($C_5H_{10}NO^+$, 10%)

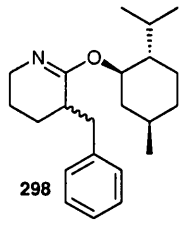
## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3,4,5,6-tetrahydro-3-methylpyridine 297




Reaction of **288** (0.0977 g, 0.41 mol) in THF (5 ml) with $^{n}$BuLi (0.43 ml, 1.03 mmol) and methyl iodide (0.1 ml, 1.23 mmol) according to general procedure D afforded the title compound **297** as a clear oil (0.0969 g, 0.339 mmol) in 94% yield and 57% d.e.; $\nu_{max}/cm^{-1}$ 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.70 (3H, d, *J* 7.0 Hz), 0.74-0.82 (8H, bm), 0.98 (1H, m), 1.06 (3H, d, *J* 7.1 Hz, 3 x H1''), 1.32-1.66 (7H, bm), 1.71-1.93 (2H, bm), 1.94-2.12 (1H, bm), 2.17 (1H, q, *J* 7.0 Hz, 1 x H5), 3.26-3.45 (2H, m, 2 x H2), 4.58 (1H, td, *J* 10.7, 4.3 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 15.1, 17.5, 19.8, 20.0, 21.0, 22.7, 25.4, 28.1, 30.1, 30.1 33.8, 39.6, 46.2, 46.6, 70.9, 163.5; *m/z* (EI) 236 ($M^+$-Me, 1%), 208 ($M^+$-$C_3H_7$, 10%), 114 ($C_5H_{10}NO^+$, 100%)

Data identifiable for the minor diastereomer; 0.67 (3H, m), 1.09 (3H, d, *J* 7.1 Hz, 3 x H1''), 4.53 (1H, td, *J* 10.7, 4.3 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 14.9, 17.5, 19.8, 19.9, 22.1, 24.6, 28.2, 30.6, 71.0; *m/z* (EI) 236 ($M^+$-Me, 1%), 208 ($M^+$-$C_3H_7$, 10%), 114 ($C_5H_{10}NO^+$, 100%)

## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3-benzyl-3,4,5,6-tetrahydropyridine 298

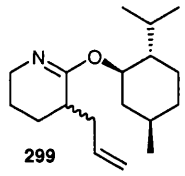



Reaction of **288** (0.1089 g, 0.46 mol) in THF (5 ml) with $^{n}$BuLi (0.5 ml, 1.15 mmol) and benzyl bromide (0.16 ml, 1.38 mmol) according to general procedure D afforded

the title compound **298** as a crude oil (0.3504g, 0.339 mmol) in a 94% yield and 37% d.e. The crude product was purified by silica gel chromatography (3% EtOAc/petrol) to afford the title compound as a clear oil (0.6224 g, 0.19 mmol), in a 41% yield and 37% d.e.; $\nu_{max}/cm^{-1}$ 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.66-0.79 (11H, bm), 0.95 (1H, m), 1.18-1.59 (8H, bm), 1.81 (1H, m, 1 x H7'), 2.01 (1H, m), 2.25-2.37 (1H, bm, 1 x H5), 2.43 (1H, dd, *J* 13.0, 10.0 Hz, 1 x H1''), 3.05 (1H, dd, *J* 13.0, 4.0 Hz, 1 x H1''), 3.27-3.33 (2H, bm, 2 x H5), 4.58 (1H, td, *J* 11.0, 4.0 Hz, 1 x H1'), 7.02-7.3 (5H, bm, $H_{Ar}$); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.1, 21.1, 21.3, 22.6, 24.3, 25.5, 27.0, 31.6, 34.0, 38.3, 38.4, 41.1, 47.5, 48.1, 72.8, 126.4, 128.8, 129.1, 138.2, no carbonyl peak observed; *m/z* (EI) 312 ($M^+$-Me, 1%), 284 ($M^+$-$C_3H_7$, 3%), 190 ($C_5H_{10}NO^+$, 100%), 172 ($C_{12}H_{14}N^+$, 23%), 95 ($C_6H_9N^+$, 32%), 77 ($Ph^+$, 6%).

Data observed for the minor diastereomer; 0.65 (3H, m), 2.42 (1H, dd, *J* 13.0, 10.0 Hz, 1 x H1''), 3.20 (1H, dd, *J* 13.0, 4.0 Hz, 1 x H1''), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.6, 21.5, 23.5, 38.4; *m/z* (EI) 284 ($M^+$-$C_3H_7$, 3%), 190 ($C_5H_{10}NO^+$, 100%), 172 ($C_{12}H_{14}N^+$, 23%), 95 ($C_6H_9N^+$, 32%), 77 ($Ph^+$, 6%).

## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3-allyl-3,4,5,6-tetrahydropyridine 291c/292c



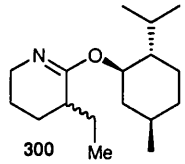

299

Reaction of **288** (0.0412 g, 0.17 mmol) in THF (2 ml) with $^n$BuLi (0.18 ml, 0.43 mmol) and allyl bromide (0.05 ml, 0.51 mmol) according to general procedure D afforded the title compound **299** as an oil (0.0467g, 0.168 mmol) in a 98% yield and 45% d.e.; (0.6224 g, 0.19 mmol); $\nu_{max}/cm^{-1}$ 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.65-0.76 (12H, bm), 0.94 (1H, m), 1.06-1.69 (7H, bm), 1.80 (1H, m, 1 x H7'), 1.94 (1H, m), 2.03-2.17 (2H, bm), 2.26-2.35 (1H, bm), 2.38-2.47 (1H, bm), 3.30 (2H, t, *J* 5.6 Hz, 2 x H2), 4.55 (1H, td, *J* 10.7, 4.3 Hz, 1 x H3'), 4.90 (1H, dm, J 10.0 Hz, 1 x H1'$^{cis}$), 4.93 (1H, dm, *J* 17 Hz, 1 x H1'$^{trans}$), 5.62 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, 1 x H2'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.1, 21.3, 21.4, 23.0, 24.1, 25.8, 26.8, 30.7, 35.0, 36.8,

37.0, 41.0, 47.5, 48.0, 72.2, 117.0, 136.8, 163.5; *m/z* (EI) 262 ($M^+$-Me, 1%), 234 ($M^+$-$C_3H_7$, 3%), 140 ($C_5H_{10}NO^+$, 100%), 122 ($C_8H_{12}N^+$, 15%),

Data observed for minor diastereomer; $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.61 (3H, m), 5.51 (1H, ddq, *J* 17.0, 10.0, 7.0 Hz, 1 x H2'), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.4, 20.9, 21.3, 24.0, 26.2, 36.9, 37.0, 47.1, 48.0, 77.9, 136.9, 163.1; *m/z* (EI) 262 ($M^+$-Me, 1%), 234 ($M^+$-$C_3H_7$, 3%), 140 ($C_5H_{10}NO^+$, 100%), 122 ($C_8H_{12}N^+$, 15%),

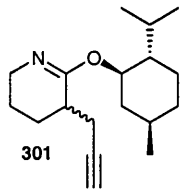
## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3-ethyl-3,4,5,6-tetrahydropyridine 300




Reaction of **288** (0.1088 g, 0.46 mmol) in THF (5 ml) with $^n$BuLi (0.48 ml, 1.15 mmol) and ethyl bromide (0.1 ml, 1.37 mmol) according to general procedure D afforded the title compound **300** as an oil (0.1197 g, 0.45 mmol) in a 98% yield and 46% d.e.; $\nu_{max}/cm^{-1}$ 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.69-0.83 (10H, bm), 0.88-2.17 (18H, bm), 3.50 (2H, t, *J* 5 Hz, 2 x H2), 4.60 (1H, td, *J* 10.5, 4.3 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.3, 21.6, 21.8, 22.1, 24.2, 25.4, 25.7, 25.8, 26.7, 34.6, 35.1, 37.4, 41.0, 47.5, 47.2, 73.4, 164.3; *m/z* (EI) 222 ($M^+$-$C_3H_7$, 7%), 128 ($C_7H_{14}NO^+$, 100%).

Data for the minor diastereomer: $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 21.8, 22.0, 24.1, 25.6, 25.7, 25.8, 35.0, 38.1, 164.1; *m/z* (EI) 222 ($M^+$-$C_3H_7$, 7%), 128 ($C_7H_{14}NO^+$, 100%).

## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3,4,5,6-tetrahydro-3-(prop-2-ynyl)pyridine 301

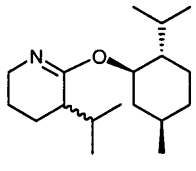



301

Reaction of **288** (0.1078 g, 0.45 mmol) in THF (5 ml) with $^{n}$BuLi (0.47 ml, 1.14 mmol) and 80 % propargyl bromide in toluene solution (0.15 ml, 1.36 mmol) according to general procedure D afforded the title compound **301** as an oil (0.1140 g, 0.414 mmol) in a 92% yield and 38% d.e.; $\nu_{max}/cm^{-1}$ 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.63-0.80 (12H, bm), 0.92 (1H, m), 1.20 (1H, m), 1.26-1.87 (6H, bm), 1.85 (1H, t, *J* 2.5 Hz, 1 x H1''), 1.88-2.08 (2H, bm), 2.25-2.36 (2H, bm), 2.39-2.52 (1H, bm, 1 x H5), 3.33 (2H, t, *J* 5.5 Hz, 2 x H2), 4.53 (1H, td, *J* 11.0, 4.3 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.2, 21.4, 21.7, 22.1, 23.0, 24.1, 26.2, 26.3, 32.3, 35.0, 35.7, 40.8, 47.5, 48.1, 70.2, 72.9, 82.7, 165.0; *m/z* (EI) 260 ($M^+$-Me, 1%), 232 ($M^+$-$C_3H_7$, 10%), 138 ($C_8H_{12}NO^+$, 100%), 122 ($C_8H_{12}N^+$, 15%), 120 ($C_8H_{10}N^+$, 6%).

Data noted for the minor diastereomer: $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.1,21.6, 22.0, 24.1, 41.2, 47.2, 70.2, 72.9, 82.6, 164.8

## 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-3,4,5,6-tetrahydro-3-isopropylpyridine 302

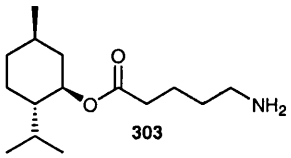



302

Reaction of **288** (0.1008 g, 0.42 mmol) in THF (5 ml) with $^{n}$BuLi (0.44 ml, 1.06 mmol) and $^{i}$propyl bromide (0.13 ml, 1.27 mmol) according to general procedure D afforded the title compound **302** as an oil (0.1018 g, 0.36 mmol) in a 86% yield and 61% d.e.;

$\nu_{max}/cm^{-1}$ 1674 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.66-0.76 (6H, bm), 0.78-0.87 (8H, bm), 0.99 (1H, m), 1.07-2.30 (14H, bm), 2.32 (1 H, m), 3.38 (2H, t, *J* 6.0 Hz, 2 x H2), 4.60 (1H, td, *J* 10.9, 4.0 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.2, 21.4, 21.7, 22.1, 23.0, 24.1, 26.2, 26.3, 32.3, 35.0, 35.7, 40.8, 47.5, 48.1, 70.2, 72.9, 82.7, 165.0; *m/z* (EI) 260 ($M^+$-Me, 1%), 232 ($M^+$-$C_3H_7$, 10%), 138 ($C_8H_{12}NO^+$, 100%), 122 ($C_8H_{12}N^+$, 15%), 120 ($C_8H_{10}N^+$, 6%).

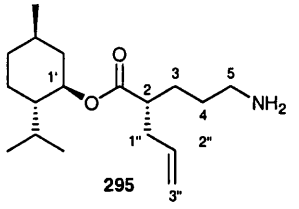
## (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 5-aminopentanoate 293



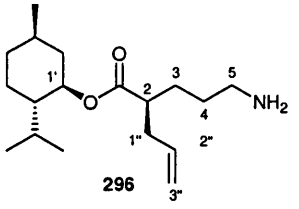
303

To a solution of **288** (0.0247 g, 0.10 mmol) in $CHCl_3$ (0.5 ml) was added 0.1M HCl (1.6 ml, 0.16 mmol) and the reaction mixture stirred vigorously for 16 hours. The reaction was quenched using sodium carbonate (0.016 g, 0.15 mmol). The reaction was concentrated *in vacuo* and extracted with $CHCl_3$ to yield then title compound **293** as an oil (0.0241 g, 0.09 mmol) in 94% yield; $\nu_{max}/cm^{-1}$ 1747 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.69-0.1.07 (12H, bm), 1.29 (1H, m), 1.34-1.47 (3H, bm), 1.52-1.66 (4H, bm), 1.78 (1H, app heptd, *J* 7.0 2.5 Hz, 1 x H7'), 1.90 (1H, dm, *J* 12.0 Hz), 2.24 (2H, t, *J* 7.0 Hz, 2 x H2), 2.62 (2H, t, *J* 7.0 Hz, 2 x H5), 4.61 (1H, td, *J* 10.9, 4.5 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 14.2, 18.6, 19.9, 20.3, 21.2, 24.1, 29.2, 31.0, 32.1, 33.3, 38.8, 39.4, 44.9, 71.9, 171.1

## (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(3-aminopropyl)pent-4-enoate 295/296



295

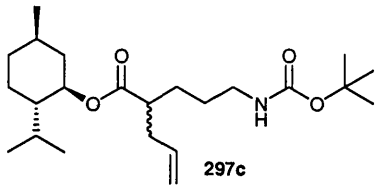


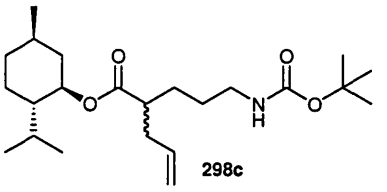
296

To a solution of **291c/292c** (0.1014 g, 0.365 mmol) in THF (5 ml) was added 0.1M HCl (5.5 ml, 0.55 mmol) and the reaction mixture stirred vigorously for 16 hours. The

reaction was quenched using sodium carbonate (0.12 g, 0.83 mmol). The reaction was concentrated *in vacuo* and extracted with $CHCl_3$ to yield the title compounds **295/296** as an oil, (0.1127 g, 0.332 mmol), in 91% yield; $\nu_{max}/cm^{-1}$ 1735 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.68-1.66 (19H, bm), 1.75-1.93 (3H, m), 2.14-2.43 (3H, bm), 2.97-3.10 (2H, m, 2 x H5), 4.60 (1H, td, *J* 11.0 and 4.3 Hz, 1 x H1'), 4.95 (1H, dm, *J* 9.0 Hz, 1 x H3''$^{cis}$), 4.99 (1H, dm, *J* 16.0 Hz, 1 x H 3''$^{trans}$), 5.65 (1H, ddt, *J* 17.0, 10.0, 6.8 Hz, 1 x H2'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 18.1, 18.6, 19.2, 21.1, 22.3, 23.6, 27.0, 27.2, 30.7, 33.1, 33.7, 39.7, 44.2, 44.3, 47.7, 74.4, 84.9, 175.0.

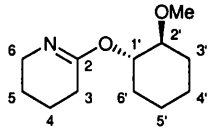
## (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(3-(tert-butoxycarbonyl)propyl)pent-4-enoate 297c/298c


297c


298c

To a solution of **291c/292c** (0.1127 g, 0.332 mmol) in MeCN (5 ml) was BOC anhydride (0.9614 g, 0.432 mmol) and triethylamine (0.68 g, 0.665 mmol) and the reaction mixture stirred vigorously for 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound **297c/298c** (0.1195 g, 0.302 mmol) in 91% yield as a clear oil; $\nu_{max}/cm^{-1}$ 1742 (C=O), 1690 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.66 (2H, app dd, *J* 7.2 and 3.2 Hz), 0.82 (2H, app d, *J* 1.7 Hz), 0.84 (4H, app d, *J* 1.2 Hz), 0.86-1.27 (4H, bm), 1.32 (9H, s, $^tBu$), 1.35-1.66 (7H, bm) 1.75-1.93 (3H, m), 2.06-2.39 (3H, bm), 2.97-3.10 (2H, m, 2 x H5), 4.50 (1H, bs, N*H*), 4.60 (1H, td, *J* 11.0 and 4.3 Hz, 1 x H1'), 4.95 (1H, dm, *J* 9.0 Hz, 1 x H3''$^{cis}$), 4.99 (1H, dm, *J* 16.0 Hz, 1 x H 3''$^{trans}$), 5.65 (1H, ddt, *J* 17.0, 10.0, 6.8 Hz, 1 x H2'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.4, 21.2, 22.4, 23.5, 26.3, 27.8, 28.8, 29.1, 29.5, 31.8, 34.6, 37.0, 40.7, 41.3, 45.6, 47.3, 74.6, 117.3, 135.7, 156.3, 175.3.

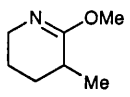
## 6-((1*S*,2*S*)-2-methoxycyclohexyloxy)-2,3,4,5-tetrahydropyridine 302




**308**

A solution of valerolactim ether **15** (2.1125 g, 18.56 mmol) and (1*S*,2*S*)-2-methoxycyclohexanol (3.1417 g, 24.13 mmol) in toluene (50 ml) was allowed to stand in the presence of 5Å molecular sieves (2.51 g) for 30 minutes. Trifluoroacetic acid (1.9 ml, 24.87 mmol) was added to the solution and allowed to stir for 18 hours. 1M $K_2CO_3$ solution (4.01 g, 31.3 mmol) was added to the reaction mixture and the reaction was extracted with $Et_2O$ (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product which was purified by Kügelrohr distillation to afford the title compound **302** as a clear oil (2.0800 g, 9.83 mmol) in 53% yield; $[\alpha]_D^{25}$ –86.1 (*c* 0.71 EtOAc); $\nu_{max}/cm^{-1}$ 1681 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 1.04-1.36 (4H, bm, 2 x H4' and 2 x H5'), 1.43-1.70 (6H, bm, 2 x H4, 2 x H5 and 2 x H3'), 1.89-2.20 (4H, bm, 2 x H3 and 2 x H6'), 3.11 (1H, ddd, *J* 9.6, 8.5 and 4.1 Hz, 1 x H2'), 3.33 (3H, s, OMe), 3.39 (2H, tt, *J* 5.6 and 1.2 Hz, 2 x H6), 4.71 (1H, ddd, *J* 9.6, 8.5 and 4.9 Hz, 1 x H1'); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 20.9, 22.9, 23.7, 23.9, 26.9, 29.9, 30.0, 47.1, 57.7, 74.1, 81.4, 161.9; *m/z* (CI) 212.1642 ($M\text{-}H^+$ requires 212.1642) 212 (100%).

## 2,3,4,5-tetrahydro-6-methoxypyridine 224[183]

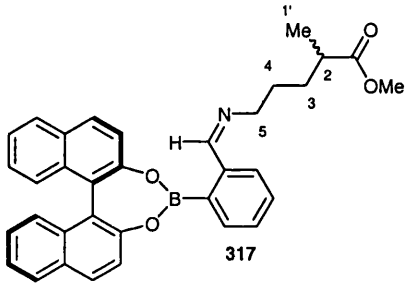



**254**

A 2.2M solution of $^nBuLi$ in hexanes (1.4 ml, 2.94 mmol) was added dropwise to a stirred solution of (-)-sparteine (0.70 g, 2.94 mmol) at -78 °C and allowed to stir under a nitrogen atmosphere. After 30 minutes a precooled solution of valerolactim ether **15** (0.2578 g, 2.27 mmol) in THF (2 ml) was added, the reaction mixture was then allowed to warm to room temperature and to stir for 60 minutes before being cooled to -78 °C.

The methyl iodide (0.55 ml, 8.79 mmol) was then added dropwise to the stirred solution and allowed to warm to room temperature over 16 hours. Alkaline water (pH >8 *via* $K_2CO_3$) was added and the reaction extracted with $Et_2O$ (x 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. The product was purified *via* Kügelrohr distillation to afford the title product **224** (0.2107 g, 1.65 mmol) as a clear oil in 73% yield. Spectroscopic data matched that of an authentic sample of α-methyl valerolactim ether *rac*-**224**.

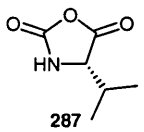
## Methyl 5-((2-((*S*)-naphtho[18,19,1,2-def][1,3,2]dioxaborepin-4-yl)phenyl)methyleneamino)hexanoate 317




317

Caesium carbonate (0.0394 g, 121 mmol), (*S*)-BINOL (0.0355 g, 122 mmol) and 2-formyl boronic acid (0.0185 g, 121 mmol) were added to a solution of **253** (0.0159 g, 0.110 mmol) in $CDCl_3$ (2 ml) containing 3Å molecular sieves (0.10 g) and the reaction mixture was allowed to stir for 20 minutes. The reaction mixture was then filtered and used for NMR analysis directly. $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.85 (3H, d, *J* 7.0 Hz, 3 x H1'), 0.87 (3H, d, *J* 7.0 Hz, 3 x H1'), 0.96-1.72 (8H, bm, 4 x H3 and 4 x H4), 2.08-2.24 (2H, m, 2 x H2), 3.33-3.59 (4H, bm, 4 x H5), 3.50 (3H, s, OMe), 3.51 (3H, s, OMe), 6.62-7.91 (32H, bm, 32 x $H_{AR}$), 8.27 (1H, s, 1 x HC=N), 8.28 (1H, s, 1 x HC=N).

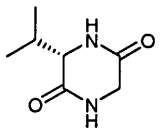
## (*S*)-4-isopropyloxazolidine-2,5-dione 287[130]




287

Phosgene (200 ml, 20% solution by weight in toluene, 0.39 mol) was added to a stirred suspension of L-valine (41.12 g, 0.35 mol) in THF (350 ml) and the reaction mixture slowly heated to 55 °C. After 4 hours the reaction mixture was cooled and the excess phosgene removed by bubbling nitrogen gas through the solution. The exhaust gases were passed through a solution of excess aqueous sodium hydroxide. The solvent was removed *in vacuo* to afford a **287** as a white crystalline solid (50.81 g, 0.35 mol) in 91% yield. $[\alpha]_D^{25}$ -44.0 (*c* 1.0 in THF) [lit.[130] -44.2 (*c* 1.0 in THF)]; $\delta_H$(300 MHz, $D_2O$) 1.03 (3H, d, *J* 7.0 Hz, 3 x H2'), 1.11 (3H, d, *J* 7.0 Hz, 3 x H2'), 2.28 (1H, m, 1 x H1'), 4.25 (1H, d, *J* 4.0 and 6.8 Hz, 1 x H4), 7.01 (1H, bs, NH).

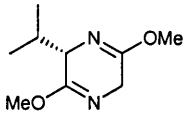
## (*S*)-3-isopropylpiperazine-2,5-dione 23[130]



**23**

Triethylamine (75 g, 0.75 mol) was added to a mechanically stirred suspension of glycine methyl ester hydrochloride (47.34 g, 0.37 mol) in chloroform (300 ml) under nitrogen and the reaction mixture cooled to -78 °C. A solution of (*S*)-4-isopropyloxazolidine-2,5-dione **287** (50.80 g, 0.35 mol) in THF (200 ml) was added dropwise over a period of two and a half hours, the reaction mixture was then stirred for a further hour at -78 °C. The crude reaction mixture was then filtered through Celite® and the filtrate concentrated *in vacuo* to afford a crude oil which was redissolved in THF (200 ml). Further filtration through Celite® and concentration *in vacuo* afforded a colourless oil, which was dissolved in toluene (200 ml) and heated to reflux. After 24 hours the residual solvent was removed *via* decantation and the remaining toluene removed *in vacuo* the resulting solid was powdered and dried for 24 hours at 110 °C under vacuum to afford the title compound **23** as a white powder (39.36 g, 0.25 mol) in 72% yield. $[\alpha]_D^{25}$ +23.1 (*c* 1.0 in $H_2O$), [lit.[130] $[\alpha]_D^{25}$ +23.7 (*c* 1.0 in $H_2O$)]; $^1$H NMR $\delta_H$(300 MHz, $D_2O$) 0.90 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.00 (3H, d, *J* 7.0 Hz, 3 x H1'), 2.25 (1H, m, 1 x H2'), 3.80 (1H, d, *J* 3.8 Hz, 1 x H3), 3.95 (1H, d, *J* 18.2 Hz, 1 x H6), 4.12 (1H, dd, *J* 19.2 and 1.2 Hz, 1 x H6); $\delta_C$(75 MHz, $D_2O$) 16.6, 18.8, 33.7, 44.6, 60.7, 169.7, 171.1.

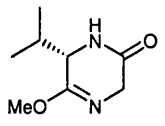
## (*S*)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 203[130]




**203**

Trimethyloxonium tetrafluoroboronate **221** (13.5 g, 91.5 mmol) was added to a vigorously stirred suspension of diketopiperazine **23** (5.0 g, 32.0 mmol) in DCM (30 ml) under an atmosphere of nitrogen and allowed to stir for 24 hours. Saturated $K_2CO_3$ (19.2 g, 150 mmol) was then added to the reaction mixture as a slurry in water (20 ml) which was allowed to slowly stir for a further hour. The reaction mixture was then diluted with water (100 ml) and DCM (100 ml) and the organic layer extracted with DCM (3 x 50 ml). The combined organic extracts filtered through Celite®, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **321** as a light yellow oil (12.1413 g, 65.9 mmol) in 72% yield. $[\alpha]_D^{23}$ +105.1 (*c* 1.0 in EtOH) [lit.[130] $[\alpha]_D^{23}$ +108.9 (*c* 1.0 in EtOH)]; $\nu_{max}/cm^{-1}$ 1694 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.68 (3H, d, *J* 6.8 Hz, 3 x H1'), 0.96 (3H, d, *J* 6.8 Hz, 3 x H1'), 2.16 (1H, app ddq, *J* 14.0, 6.8, 3.5 Hz, 1 x H2'), 3.61 (3H, s, OMe $C_6$), 3.65 (3H, s, OMe $C_3$), 3.89-3.97 (3H, m, 1 x H5 and 2 x H2); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.8, 18.9, 32.3, 46.4, 52.3, 52.4, 60.8, 162.2, 164.7; *m/z* (CI) 185.1285 ($M\text{-}H^+$ requires 185.1284) 185 (100%)

## (*S*)-6-isopropyl-5-methoxy-1,6-dihydropyrazin-2(3H)-one 335

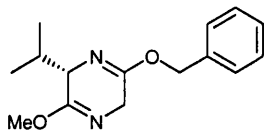



**335**

$d_1$-acetic acid (5 g, 81.9 mmol) was added to **203** (0.2537 g, 1.38 mmol) and allowed to stir for 16 hours. 1M $K_2CO_3$ solution (13.15 g, 102.8 mmol) was added to the reaction mixture and the reaction was extracted with $Et_2O$ (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **335** as clear solid (0.1891 g, 1.11 mmol) in 81% yield. mp = 45 °C; $[\alpha]_D^{23}$ +8.8 (*c* 1.0 in

$H_2O$) [lit.[130] $[\alpha]_D^{23}$ +9.1 (*c* 1.0 in $H_2O$)]; $\nu_{max}/cm^{-1}$ 3240 (NH), 1702 (C=N), 1676 (C=O); $\delta_H$(300MHz, MeOD) 0.92 (3H, d, *J* 7.0 Hz, 3 x H1'), 1.00 (3H, d, *J* 7.0 Hz, 3 x H1'), 2.20 (1H, m, 1 x H2'), 3.75 (3H, s, OMe), 3.95 (1H, m, 1 x H5), 4.07 (2H, m, 2 x H2); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.9, 18.6, 34.2, 50.5, 53.6, 59.5, 162.7, 171.7; *m/z* (CI) 171.1134 ($M-H^+$ requires 174.1139) 174 (100%)

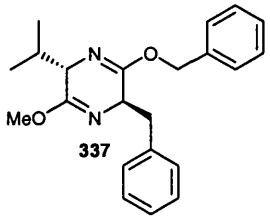
## (*S*)-6-(benzyloxy)-2,5-dihydro-2-isopropyl-3-methoxypyrazine 328




328

A solution of **203** (1.1589 g, 6.23 mmol) and benzyl alcohol (0.8748 g, 8.10 mmol) in toluene (20 ml) was allowed to stand in the presence of 5Å molecular sieves (1.1 g) for 30 minutes. Trifluoroacetic acid (0.62 ml, 8.10 mmol) was added to the solution and allowed to stir for 18 hours. 1M potassium carbonate solution (1.54 g, 12.1 mmol) was added to the reaction mixture and the reaction was extracted with $Et_2O$ (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil, which was purified by Kügelrohr distillation to afford the title compound as a clear oil (0.8612 g, 3.32 mmol) in 53% yield. $[\alpha]_D^{23}$ 175.1 (*c* 1.0 in EtOH); $\nu_{max}/cm^{-1}$ 1699 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.63 (3H, d, *J* 6.9 Hz, 3 x H1'), 0.94 (3H, d, *J* 6.9 Hz, 3 x H1'), 2.17 (1H, ddq, *J* 20.6, 6.9 and 3.4 Hz, 1 x H2'), 3.61 (3H, s, OMe), 3.89-4.11 (3H, m, 2 x H2 and 1 x H5), 4.98 (1H, d, *J* 12.3 Hz, 1 x H1''), 5.18 (1H, d, *J* 12.3 Hz, 1 x H1''), 7.18-7.34 (5H, bm, 5 x $H_{Ar}$); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 17.3, 19.5, 32.7, 47.2, 53.0, 61.5, 67.2, 128.2, 128.4, 128.8, 137.5, 161.9, 165.1; *m/z* (CI) 261.1595 ($M-H^+$ requires 261.1598) 261 (91%), 171 (-Bn, 100), 108 (OBn, 46).

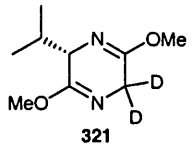
## (2*R*,5*S*)-2-benzyl-3-(benzyloxy)-2,5-dihydro-5-isopropyl-6-methoxypyrazine 337



337

Reaction of **321** (0.0101 g, 0.039 mmol) in THF (10 ml) with 2.36M $^{n}$BuLi in hexanes (0.5 ml, 1.18 mmol) and benzyl bromide (0.16 ml, 1.40 mmol) in THF (2 ml) according to general procedure G afforded the title compound **347** as a crude product in >95% d.e. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.0109 g, 0.031 mmol) in a 80% yield and >90% d.e.; $[\alpha]_D^{25}$ 111.2 (*c* 1.3 in EtOH); $\nu_{max}/cm^{-1}$ 1691 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.47 (3H, d, *J* 6.9 Hz, 3 x H1'), 0.86 (3H, d, *J* 6.9 Hz, 3 x H1'), 2.05 (1H, m, 1 x H2'), 3.05 (2H, dd, *J* 8.3 and 3.4 Hz, 2 x H1''), 3.13 (1H, app t, *J* 3.4 Hz, 1 x H5), 3.61 (3H, s, OMe), 4.33 (1H, dd, *J* 4.7 and 3.8 Hz, 1 x H2), 5.10 (1H, d, *J* 12.4 Hz, 1 x OC*H*H), 5.04 (1H, d, *J* 12.4 Hz, 1 x OCH*H*), 6.95-6.99 (2H, m, 2 x $H_{Ar}$), 7.07-7.13 (3H, m, 3 x $H_{Ar}$), 7.22-7.38 (5H, m, 5 x $H_{Ar}$); $\delta_C$(75MHz, MeOD, $Me_4Si$) 15.3, 18.1, 29.9, 38.9, 51.4, 55.6, 59.2, 65.5, 125.3, 126.7, 126.8, 127.1, 127.4, 129.0, 136.1, 136.3, 160.6, 163.0.

## (*S*)-2,2-dideutero-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 321[173]

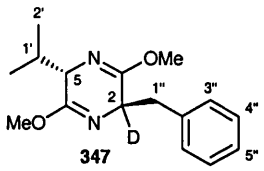


321

A solution of **203** (12.54 g, 67.4 mmol) in $d_1$-methanol (25 ml) was allowed to stand in the presence of 4Å molecular sieves (9.6 g) for 30 minutes. Trifluoroacetic acid (6.85 ml, 87.65 mmol) was added to the solution and allowed to stir for 18 hours. 1M $K_2CO_3$ solution (14.38 g, 112.4 mmol) was added to the reaction mixture and the reaction was extracted with $Et_2O$ (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **321** (11.53 g, 62.0 mmol) in 92% yield. $[\alpha]_D^{23}$ 72.0 (*c* 1.0 in EtOH) [lit.[173] $[\alpha]_D^{23}$ 65.6 (*c* 1.38 in EtOH)]; $\nu_{max}/cm^{-1}$

1694 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.68 (3H, d, *J* 6.8 Hz, 3 x H1'), 0.96 (3H, d, *J* 6.8 Hz, 3 x H1'), 2.16 (1H, m, 1 x H2'), 3.61 (3H, s, OMe), 3.65 (3H, s, OMe), 3.92 (1H, d, *J* 3.5 Hz, 1 x H5); $\delta_D$(60MHz, $CHCl_3$) 3.99 (1D, d, *J* 3.1 Hz, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.8, 18.9, 32.3, 52.3, 52.4, 60.8, 162.2, 164.7; *m/z* (CI) 187.1409 (M-$H^+$ requires 187.1410) 187 (62%), 173 (-Me, 100).

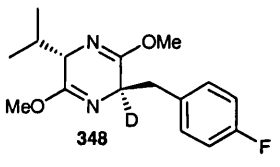
## (2*R*,5*S*)-2-benzyl-2,5-dihydro-2-deutero-5-isopropyl-3,6-dimethoxypyrazine 347[173]



347

Reaction of **321** (0.2000 g, 1.08 mmol) in THF (10 ml) with 2.36M $^n$BuLi in hexanes (0.5 ml, 1.18 mmol) and benzyl bromide (0.16 ml, 1.40 mmol) in THF (2 ml) according to general procedure H afforded the title compound **347** as a crude product in >90% d.e. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.2379 g, 0.864 mmol) in a 80% yield and >95% d.e.; $[\alpha]_D^{25}$ 41.2 (*c* 1.3 in $CH_2Cl_2$) [lit.[173] 40.4 (*c* 1.55 $CH_2Cl_2$)] ; $\nu_{max}/cm^{-1}$ 1681 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.53 (3H, d, *J* 6.8 Hz, 3 x H1'), 0.87 (3H, d, *J* 6.8 Hz, 3 x H1'), 2.07 (1H, m, 1 x H2'), 3.01 (2H, app s, 2 x H1''), 3.18 (1H, d, *J* 3.2 Hz, 1 x H5), 3.61 (3H, s, OMe), 3.65 (3H, s, OMe), 6.99-7.20 (5H, bm, 5 x $H_{Ar}$); $\delta_C$(75MHz, MeOD, $Me_4Si$) 16.8, 19.4, 31.5, 40.3, 52.5, 52.8, 60.6, 126.7, 128.2, 130.4, 137.7, 162.8, 164.4; *m/z* (CI) 276.1814 (M-$H^+$ requires 276.1817) 276 (100%).

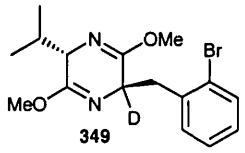
## (2*R*,5*S*)-2-(4-fluorobenzyl)-2-deutero-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 348



348

Reaction of **321** (0.2000 g, 1.08 mmol) in THF (10 ml) with 2.36M $^{n}$BuLi in hexanes (0.5 ml, 1.18 mmol) and *p*-fluoro-benzyl bromide (0.17 ml, 1.40 mmol) in THF (2 ml) according to general procedure H afforded the title compound **348** as a crude product in >90% d.e. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.2249 g, 0.767 mmol) in a 71% yield and >95% d.e.; $[\alpha]_D^{27}$ +62.4 (*c* 1.0 in EtOAc); $\nu_{max}/cm^{-1}$ 1694 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.53 (3H, d, *J* 6.8 Hz, 3 x H1'), 0.88 (3H, d, *J* 6.8 Hz, 3 x H1'), 2.08 (1H, m, 1 x H2'), 2.98 (2H, app t, *J* 14 Hz, 2 x H1''), 3.25 (1H, d, *J* 3.0 Hz, 1 x H5), 3.59 (3H, s, OMe), 3.63 (3H, s, OMe), 6.82 (2H, app t, *J* 8.1 Hz, 2 x H4''), 6.97 (2H, dd, *J* 7.7, 5.8 Hz, 2 x H3''); $\delta_C$(75MHz, MeOD, $Me_4Si$) 16.8, 19.4, 31.6, 39.4, 52.5, 52.7, 60.7, 115.0 (d, *J* 10.5 Hz), 131.7 (d, *J* 3.8 Hz), 133.4, 162.6, 164.4[x]; *m/z* (CI) 294.1721 ($M\text{-}H^+$ requires 294.1723) 294 (32%), 278 (100, -Me), 250 (84, -$^{i}$Pr), 236 (88, -Me -$^{i}$Pr), 109 ($C_7H_6F$, 58)

## (2*R*,5*S*)-2-(2-bromobenzyl)-2-deutero-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 349



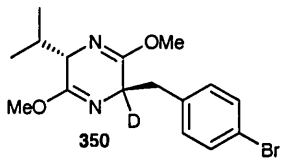
349

Reaction of **321** (0.2000 g, 1.08 mmol) in THF (10 ml) with 2.36M $^{n}$BuLi in hexanes (05 ml, 1.18 mmol) and *o*-bromo-benzyl bromide (0.3581 g, 1.41 mmol) in THF (2 ml) according to general procedure H afforded the title compound **349** as a crude product in >90% d.e. The crude product (0.2 g) was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.2793 g, 0.79 mmol) in a 73% yield and >95% d.e.; $[\alpha]_D^{25}$ -7.5 (*c* 1.0 in EtOAc); $\nu_{max}/cm^{-1}$ 1694 (C=N); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.58 (3H, d, *J* 6.8 Hz, 3 x H1'), 0.94 (3H, d, *J* 6.8 Hz, 3 x H1'), 2.14 (1H, m, 1 x H2'), 2.86 (1H, d, *J* 14.0 Hz, 1 x H1''), 3.39 (1H, d, *J* 14.0 Hz, 1 x H1''), 3.57 (3H, s, OMe), 3.66 (3H, s, OMe), 3.59 (1H, d, *J* 3.6 Hz, 1 x H5), 6.99 (1H, app ddd, *J* 9.0, 5.8 and 3.2 Hz, 1 x $H_{Ar}$), 7.06-7.26 (2H, bm, 2 x $H_{Ar}$), 7.37-7.57 (1H, m, 1 x $H_{Ar}$); $\delta_C$(75MHz, MeOD, $Me_4Si$) 16.9, 19.5, 31.8, 40.6, 52.9, 56.3, 60.8,

[x] Quaternary *para* centre not observed.

125.8, 127.2, 128.3, 132.3, 133.0, 138.2, 163.5, 164.2; *m/z* (CI) 354.0922 ($M^{79}Br\text{-}H^+$ requires 354.0921) 356 ($M^{81}Br\text{-}H^+$, 100%), 354 ($M^{79}Br\text{-}H^+$,100).

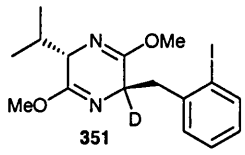
## (2*R*,5*S*)-2-(4-bromobenzyl)-2-deutero-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 350[186]



350

Reaction of **321** (0.2000 g, 1.08 mmol) in THF (10 ml) with 2.36M $^n$BuLi in hexanes (05 ml, 1.18 mmol) and *p*-bromo-benzyl bromide (0.3539 g, 1.40 mmol) in THF (2 ml) according to general procedure H afforded the title compound **350** as a crude product in >90% d.e. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.2870 g, 0.81 mmol) in a 75% yield and >95% d.e.; mp = 58-64 °C; $[\alpha]_D^{25}$ -5.2 (*c* 1.0 in EtOAc); $\nu_{max}/cm^{-1}$ 1694 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.54 (3H, d, *J* 6.8 Hz, 3 x H1'), 0.88 (3H, d, *J* 6.8 Hz, 3 x H1'), 2.08 (1H, m, 1 x H2'), 2.96 (2H, app s, 2 x H1''), 3.32 (1H, d, *J* 3.0 Hz, 1 x H5), 3.59 (3H, s, OMe), 3.63 (3H, s, OMe), 6.89 (2H, d, *J* 7.9 Hz, 2 x H4''), 7.25 (2H, d, *J* 7.9 Hz, 2 x H3''), $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 16.8, 19.4, 31.7, 39.6, 52.6, 56.7, 60.7, 120.7, 131.3, 132.0, 136.8, 162.5, 164.4; *m/z* (CI) 354.0922 ($M^{79}Br\text{-}H^+$ requires 354.0921) 356 ($M^{81}Br\text{-}H^+$, 33%), 354 ($M^{79}Br\text{-}H^+$, 36), 340 (98), 338 (100), 184 ($C_9H_{14}DN_2O_2$, 51), 142 ($C_6H_8DN_2O_2$, 100).

## (2*R*,5*S*)-2-(2-iodobenzyl)-2-deutero-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 351

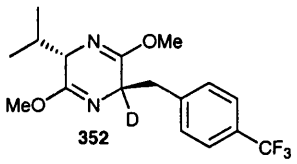


351

Reaction of **321** (0.2000 g, 1.08 mmol) in THF (10 ml) with 2.36M $^n$BuLi in hexanes (05 ml, 1.18 mmol) and *o*-iodo-benzyl bromide (0.4140 g, 1.40 mmol) in THF (2 ml)

according to general procedure H afforded the title compound **351** as a crude product in >90% d.e. The crude product (0.2 g) was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.2947 g, 0.73 mmol) in a 68% yield and >95% d.e.; $[\alpha]_D^{25}$ +15.5 (*c* 1.0 in EtOAc); $\nu_{max}/cm^{-1}$ 1692 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.58 (3H, d, *J* 7.0 Hz, 3 x H1'), 0.94 (3H, d, *J* 7.0 Hz, 3 x H1'), 2.15 (1H, m, 1 x H2'), 2.86 (1H, d, *J* 13.6 Hz, 1 x H1''), 3.35 (1H, d, *J* 13.6 Hz, 1 x H1''), 3.57 (3H, s, OMe), 3.64 (1H, d, *J* 3.4 Hz, 1 x H5), 3.66 (3H, s, OMe), 6.80 (1H, ddd, *J* 2.6, 6.4 and 7.9 Hz, 1 x $H_{Ar}$), 7.10-7.19 (2H, bm, 2 x $H_{Ar}$), 7.73 (1H, d, *J* 7.9, 1 x $H_{Ar}$), $\delta_C$(75MHz, $CHCl_3$, $Me_4Si$) 15.5, 18.1, 30.4, 43.7, 51.5, 51.6, 59.5, 100.8, 126.7, 127.0, 130.0, 138.3, 140.2, 162.0, 162.8; *m/z* (CI) 402.0783 ($M\text{-}H^+$ requires 402.0783) 403 (17%), 358 (-iPr, 100), 274 (-I, 14), 217 ($C_7H_6Br$, 34), 184 ($C_9H_{14}DN_2O_2$, 27), 142 ($C_6H_8DN_2O_2$, 100), 127 (I, 12).

## (2*R*,5*S*)-2-(4-(trifluoromethyl)benzyl)-2-deutero-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine 352

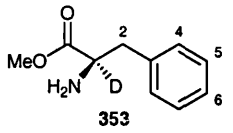


352

Reaction of **321** (0.2000 g, 1.08 mmol) in THF (10 ml) with 2.36M $^nBuLi$ in hexanes (05 ml, 1.18 mmol) and *p*-trifluoromethyl-benzyl bromide (0.3301 g, 1.40 mmol) in THF (2 ml) according to general procedure H afforded the title compound **352** as a crude product in >90% d.e. The crude product was purified by silica gel chromatography (5% EtOAc/petrol) to afford the title compound as a clear oil (0.3078 g, 0.90 mmol) in a 83% yield and >95% d.e.; mp = 57-58 °C; $[\alpha]_D^{25}$ -20.7 (*c* 1.0 in EtOAc); $\nu_{max}/cm^{-1}$ 1694 (C=N), $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 0.54 (3H, d, *J* 7.2 Hz, 3 x H2'), 0.87 (3H, d, *J* 7.2 Hz, 3 x H1'), 2.08 (1H, m, 1 x H1'), 2.99 (1H, d, *J* 13.2 Hz, 1 x H1''), 3.11 (1H, d, *J* 13.2 Hz, 1 x H1''), 3.33 (1H, d, *J* 3.2 Hz, 1 x H5), 3.58 (3H, s, OMe), 3.63 (3H, s, OMe), 7.14 (2H, d, *J* 8.0 Hz, 2 x H3''), 7.39 (2H, d, *J* 8.0 Hz, 1 x H4''), $\delta_C$(75MHz, MeOD, $Me_4Si$); 16.7, 19.3, 31.9, 40.2, 52.5, 52.7, 60.8, 124.8 (q, *J* 270 Hz), 125.0 (q, *J* 3.8 Hz), 130.6, 131.0 (q, *J* 32.3 Hz), 142.2, 162.5, 164.5; *m/z* (CI) 344.1692 ($M\text{-}H^+$ requires 344.1691) 344 (15%) 300 (-$^iPr$, 100), 329 (-Me, 33), 300 (-

$^{i}$Pr, 100), 271 (-$^{i}$Pr, -OMe, 50), 184 ($C_9H_{14}DN_2O_2$, 9) 159 ($C_8H_6F_3$, 10), 142 ($C_6H_8DN_2O_2$, 22), 69 ($CF_3$, 4).

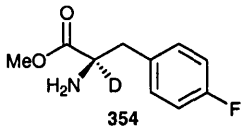
## (*R*)-methyl 2-amino-2-deutero-3-phenylpropanoate 353[187]




353

Reaction of **347** (0.0217 g, 0.12 mmol) in acetonitrile (1.2 ml) was treated with 0.3M HCl (1.2 ml, 0.36 mmol) according to general procedure I afforded the title compound **353** (0.0186 g, 0.086 mmol) as a clear oil in 72% yield; $[\alpha]_D^{25}$ 4.3 (*c* 1.0 in $H_2O$) [lit.[187] $[\alpha]_D^{23}$ 4.4 (*c* 1.02 in $H_2O$)]; $\nu_{max}/cm^{-1}$ 3412 (NH), 1740 (C=O); $\delta_H$(300MHz, $D_2O$) 3.24 (1H, d, *J* 14.5 Hz, 1 x H2), 3.35 (1H, d, *J* 14.5 Hz, 1 x H2), 3.85 (3H, s, OMe), 7.26-7.49 (5H, bm, 5 x $H_{AR}$); $\delta_D$(60MHz, EtOH) 4.22 (1D, s, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 35.7, 53.8, 128.3, 129.5, 129.7, 134.0, 170.3; *m/z* (CI) 181.1080 (M-$H^+$ requires 181.1082) 181 (100%).

## (*R*)-methyl 2-amino-2-deutero-3-(4-fluorophenyl)propanoate 354[188]



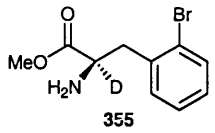

354

Reaction of **348** (0.0291 g, 0.10 mmol) in acetonitrile (1.2 ml) was treated with 0.3M HCl (1.0 ml, 0.30 mmol) according to general procedure I afforded the title compound **354** (0.0279 g, 0.119 mmol) as a clear oil in 81% yield; $[\alpha]_D^{25}$ -34.3 (*c* 1.0 in EtOH) [lit.[188] $[\alpha]_D^{23}$ -32.2 (*c* 1.0 in EtOH)]; $\nu_{max}/cm^{-1}$ 3389 (NH), 1740 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.22 (1H, d, *J* 14.0 Hz, 1 x H2), 3.32 (1H, d, *J* 14.0 Hz, 1 x H2), 3.86 (3H, s, OMe), 7.13 (2H, app t, *J* 8.1 Hz, 2 x H5), 7.31 (2H, dd, *J* 7.7, 5.8 Hz, 2 x H4); $\delta_D$(60MHz, EtOH) 4.14 (1D, s, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$)[xi] 35.0, 53.9, 116.3 (*J*

[xi] Quaternary aromatic centre resonances too weak.

21.8 Hz), 131.5 (*J* 6.8 Hz), 164.2; *m/z* (CI) 199.0987 ($M\text{-}H^+$ requires 199.0988) 199 (100%).

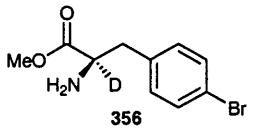
## (*R*)-methyl 2-amino-2-deutero-3-(2-bromophenyl)propanoate 355



355

Reaction of **349** (0.0213 g, 0.06 mmol) in acetonitrile (1.2 ml) was treated with 0.3M HCl (0.6 ml, 0.18 mmol) according to general procedure I afforded the title compound **355** (0.0134 g, 0.45 mmol) as a clear oil in 75% yield; $[\alpha]_D^{25}$ -3.1 (*c* 1.0 in EtOH); $\nu_{max}/cm^{-1}$ 3435 (NH), 1740 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.21 (1H, d, *J* 14.7 Hz, 1 x H2), 3.53 (1H, d, *J* 14.7 Hz, 1 x H2), 3.81 (3H, s, OMe), 7.25-7.44 (3H, bm, 3 x $H_{AR}$), 7.70 (1H, dd, *J* 7.9 and 1.0 Hz, 1 x $H_{AR}$); $\delta_D$(60MHz, $H_2O$) 4.35 (1D, s, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 34.6, 52.1, 122.7, 126.8, 128.5, 130.3, 131.8, 131.9, 168.3; *m/z* (CI) 259.0184 ($M^{79}Br\text{-}H^+$ requires 259.0187) 261 ($M^{81}Br\text{-}H^+$, 98) 259 ($M^{79}Br\text{-}H^+$,100), 181 (-Br, 43).

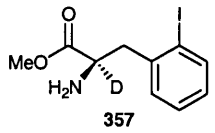
## (*R*)-methyl 2-amino-3-(4-bromophenyl)-2-deutero-propanoate 356



356

Reaction of **350** (0.0210 g, 0.06 mmol) in acetonitrile (1.2 ml) was treated with 0.3M HCl (0.6 ml, 0.18 mmol) according to general procedure I afforded the title compound **356** (0.0147 g, 0.05 mmol) as a clear oil in 83% yield; $[\alpha]_D^{25}$ 18.5 (*c* 1.0 in EtOH); $\nu_{max}/cm^{-1}$ 3420 (NH), 1740 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.21 (1H, d, *J* 14.7 Hz, 1 x H2), 3.31 (1H, d, *J* 14.7 Hz, 1 x H2), 3.84 (3H, s, OMe), 7.20 (2H, d, *J* 8.5 Hz, 2 x H5), 7.58 (2H, d, *J* 8.5 Hz, 2 x H4); $\delta_D$(60MHz, EtOH) 4.35 (1D, s, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 35.2, 53.9, 121.8, 131.5, 132.5, 133.2, 170.2; *m/z* (CI) 259.0184 ($M^{79}Br\text{-}H^+$ requires 259.0187) 261 ($M^{81}Br\text{-}H^+$, 97) 259 ($M^{79}Br\text{-}H^+$,100), 181 (-Br, 43).

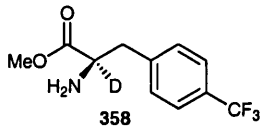
## (*R*)-methyl 2-amino-2-deutero-3-(2-iodophenyl)propanoate 357



357

Reaction of **351** (0.0256 g, 0.06 mmol) in acetonitrile (1.2 ml) was treated with 0.3M HCl (0.7 ml, 0.21 mmol) according to general procedure I afforded the title compound **357** (0.0167 g, 0.05 mmol) as a clear oil in 76% yield; $[\alpha]_D^{25}$ -13.3 (*c* 1.0 in EtOH); $\nu_{max}/cm^{-1}$ 3420 (NH), 1740 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 2.84 (1H, d, *J* 13.6 Hz, 1 x H2), 3.16 (1H, d, *J* 13.6 Hz, 1 x H2), 3.70 (3H, s, OMe), 6.87 (1H, td, *J* 7.5 and 1.5 Hz, 1 x $H_{AR}$), 7.14 (1H, dd, *J* 7.5 and 1.9 Hz, 1x $H_{AR}$), 7.22 (1H, td, *J* 7.5 and 1.1 Hz, 1 x $H_{AR}$), 7.78 (1H, dd, *J* 7.5 and 1.1 Hz, 1 x $H_{AR}$); $\delta_D$(60MHz, EtOH) 4.32 (1D, s, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$) 40.8, 54.0, 130.2, 131.2, 131.3, 132.1, 137.0, 140.5, 170.0; *m/z* (CI) 307.0049 ($M\text{-}H^+$ requires 349.0048) 307 (65%), 181 (-I, 100).

## (*R*)-methyl 2-amino-2-deutero-3-(4-(trifluoromethyl)phenyl) propanoate 358

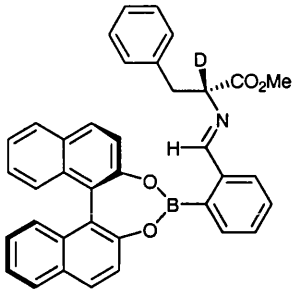


358

Reaction of **352** (0.0310 g, 0.09 mmol) in acetonitrile (1.2 ml) was treated with 0.3M HCl (0.9 ml, 0.27 mmol) according to general procedure I afforded the title compound **358** (0.0219 g, 0.08 mmol) as a clear oil in 85% yield; $[\alpha]_D^{25}$ -24.8 (*c* 1.0 in EtOH) [lit.[188] $[\alpha]_D^{25}$ 24 (for *ent* **358**) (*c* 1.0 in EtOH)]; $\nu_{max}/cm^{-1}$ 3402 (NH), 1742 (C=O); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.33 (1H, d, *J* 14.5 Hz, 1 x H2), 3.43 (1H, d, *J* 14.5 Hz, 1 x H2), 3.83 (3H, s, OMe), 7.46 (2H, d, *J* 7.9 Hz, 2 x H4), 7.74 (2H, d, *J* 7.9 Hz, 2 x H5); $\delta_D$(60MHz, EtOH) 4.23 (1D, s, 1 x D); $\delta_C$(75MHz, $CDCl_3$, $Me_4Si$)[xii] 35.6, 53.9, 126.4, 130.2; *m/z* (CI) 249.0955 ($M\text{-}H^+$ requires 249.0956) 249 (100%).

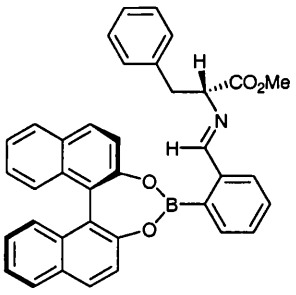
[xii] Quaternary centres too weak.

## (*S*,*E*)-methyl 2-((2-(naphtho[2,1,6,7-def][1,3,2]dioxaborepin-4-yl)phenyl)methyleneamino)-2-deutero-3-phenylpropanoate



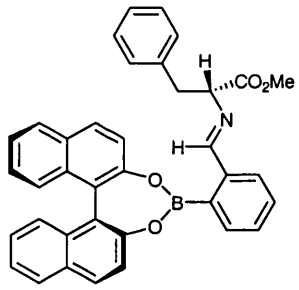

Caesium carbonate (0.0394 g, 121 mmol), (*S*)-BINOL (0.0355 g, 122 mmol) and 2-formyl boronic acid (0.0185 g, 121 mmol) were added to a solution of **353** (0.0159 g, 0.110 mmol) in $CDCl_3$ (2 ml) containing 3Å molecular sieves (0.10 g) and the reaction mixture was allowed to stir for 20 minutes. The reaction mixture was then filtered and used for NMR analysis directly; $[\alpha]_D^{25}$ -576 (*c* 1.0 in $CDCl_3$); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.07 (1H, d, *J* 13.6 Hz, 1 x H2), 3.36 (1H, d, *J* 13.6 Hz, 1 x H2), 3.77 (3H, s, OMe), 7.01-7.41 (13H, bm, 13 x $H_{Ar}$), 7.48 (1H, d, *J* 8.4 Hz, 1 x $H_{Ar}$), 7.80 (1H, d, *J* 8.7 Hz, 1 x $H_{Ar}$), 7.87-7.93 (4H, m, 4 x $H_{Ar}$), 8.03 (1H, s, *H*C=N); $\delta_c$(75 MHz, $CDCl_3$), 39.4, 53.1, 118.2, 122.7, 123.4, 123.8, 127.5, 127.9, 128.3, 128.9, 129.0, 129.3, 129.5, 130.3, 130.4, 130.8, 133.7, 133.8, 135.3, 137.3, 154.4, 154.9, 170.4, 172.0; *m/z* (EI) 562.2178 ($M\text{-}H^+$ requires 562.2176) 562 (100%).

## (*R*,*E*)-methyl 2-((2-(naphtho[2,1,6,7-def][1,3,2]dioxaborepin-4-yl)phenyl)methyleneamino)-3-phenylpropanoate



Caesium carbonate (0.0220 g, 0.66 mmol), (*S*)-BINOL (0.0181 g, 0.6 mmol) and 2-formyl boronic acid (0.0087 g, 0.6 mmol) were added to a solution of (*R*)-phenylalanine methyl ester hydrochloride (0.0131 g, 0.6 mmol) in $CDCl_3$ (4 ml) containing 3Å molecular sieves (0.10 g) and the reaction mixture was allowed to stir for 20 minutes. The reaction mixture was then filtered and used for NMR analysis directly; $[\alpha]_D^{25}$ -581 (*c* 1.0 in $CDCl_3$); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.07 (1H, dd, *J* 13.6 and 7.6 Hz, 1 x H2), 3.36 (1H, dd, *J* 13.6 and 3.3 Hz, 1 x H2), 3.77 (3H, s, OMe), 4.60 (1H, dd, *J* 7.6 and 4.8 Hz, 1 x H1), 7.01-7.41 (13H, bm, 13 x $H_{Ar}$), 7.48 (1H, d, *J* 8.4 Hz, 1 x $H_{Ar}$), 7.80 (1H, d, *J* 8.7 Hz, 1 x $H_{Ar}$), 7.87-7.93 (4H, m, 4 x $H_{Ar}$), 8.03 (1H, s, *H*C=N); $\delta_c$(75 MHz, $CDCl_3$) 39.4, 53.1, 118.2, 122.7, 123.4, 123.8, 127.5, 127.9, 128.3, 128.9, 129.0, 129.3, 129.5, 130.3, 130.4, 130.8, 133.7, 133.8, 135.3, 137.3, 154.4, 154.9, 170.4, 172.0; *m/z* (EI) 561.2108 ($M\text{-}H^+$ requires 561.2106) 561 (100%).

## (*R*,*E*)-methyl 2-((2-(naphtho[7,6,1,2-def][1,3,2]dioxaborepin-4-yl)phenyl)methyleneamino)-3-phenylpropanoate




Caesium carbonate (0.0215 g, 0.66 mmol), (*R*)-BINOL (0.0172 g, 0.6 mmol) and 2-formyl boronic acid (0.0090 g, 0.6 mmol) were added to a solution of (*R*)-phenylalanine methyl ester hydrochloride (0.0129 g, 0.6 mmol) in $CDCl_3$ (4 ml) containing 3Å molecular sieves (0.10 g) and the reaction mixture was allowed to stir for 20 minutes. The reaction mixture was then filtered and used for NMR analysis directly; $[\alpha]_D^{25}$ 336 (*c* 1.0 in $CDCl_3$); $\delta_H$(300MHz, $CDCl_3$, $Me_4Si$) 3.25 (1H, dd, *J* 13.6 and 8.6 Hz, 1 x H2), 3.41 (3H, s, OMe), 3.47 (1H, dd, *J* 13.6 and 4.8 Hz, 1 x H2), 4.61 (1H, dd, *J* 8.4 and 4.8 Hz, 1 x H1), 6.95 (1H, d, *J* 7.0 Hz, 1 x $H_{Ar}$), 7.00-7.04 (2H, m, 2 x $H_{Ar}$), 7.09-7.43 (12H, bm, 12 x $H_{Ar}$), 7.48 (1H, d, *J* 7.4 Hz, 1 x $H_{Ar}$), 7.80-7.92 (5H, m, 5 x $H_{Ar}$), 8.40 (1H, s, *H*C=N); $\delta_c$(75 MHz, $CDCl_3$) 39.7, 53.0, 60.4, 118.2, 122.4, 123.4,

123.8, 127.7, 128.8, 128.2, 128.4, 128.8, 129.3, 129.4, 129.5, 130.0, 130.3, 133.6, 134.0, 134.8, 137.3, 154.4, 154.4, 154.8, 170.6, 172.5, 172.5; *m/z* (EI) 561.2099 ($M-H^+$ requires 561.2106) 561 (100%).

# Chapter 7

# Appendix A

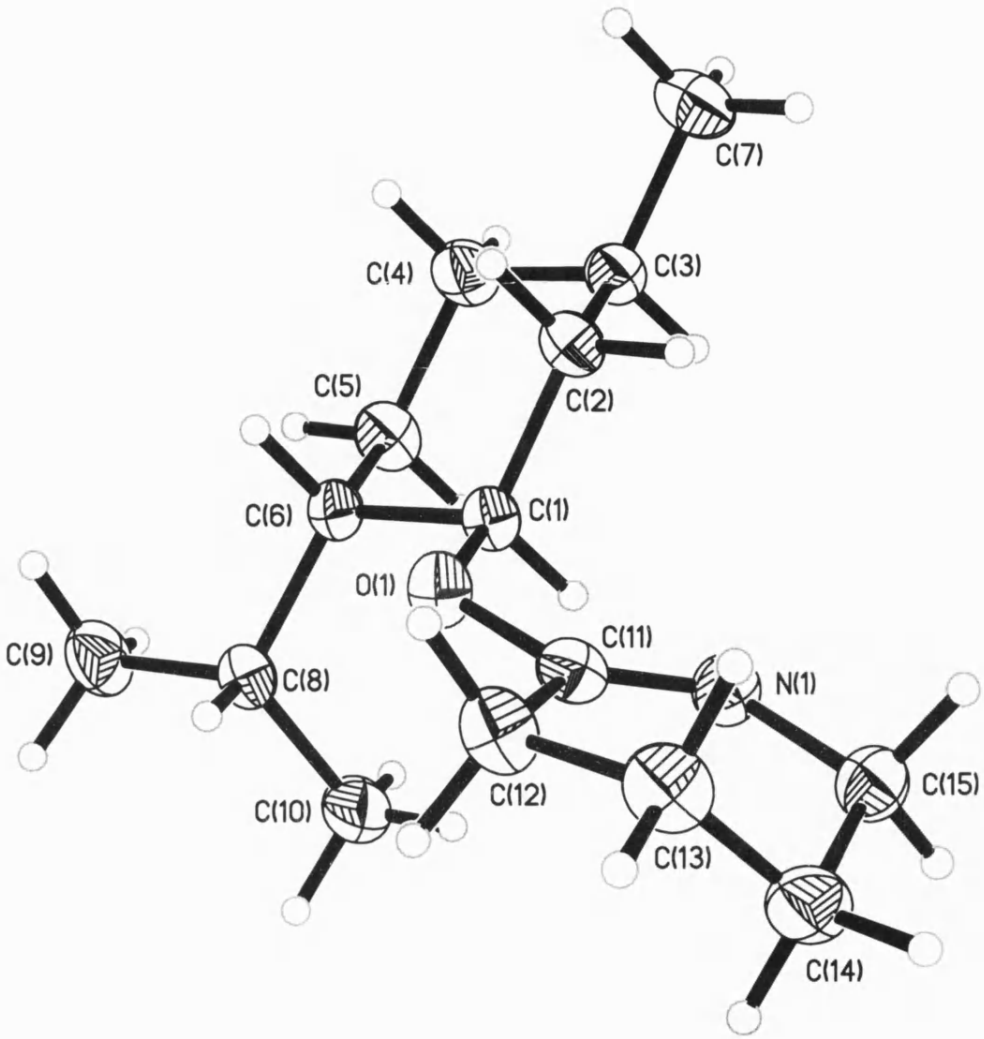

C(7)
C(4)
C(3)
C(5)
C(2)
C(6)
C(1)
O(1)
C(9)
C(11)
C(8)
N(1)
C(15)
C(10)
C(12)
C(13)
C(14)

Table 1. Crystal data and structure refinement for h03sdb01.

| | | |
|---|---|---|
| Identification code | h03sdb01 | |
| Empirical formula | C15 H27 N O | |
| Formula weight | 237.38 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | a = 8.1550(2) Å | □= 90°. |
| | b = 6.15500(10) Å | □= |
| 101.8130(10)°. | | |
| | c = 14.8540(4) Å | □ = 90°. |
| Volume | 729.79(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.080 $Mg/m^3$ | |
| Absorption coefficient | 0.066 $mm^{-1}$ | |
| F(000) | 264 | |
| Crystal size | 0.25 x 0.20 x 0.17 $mm^3$ | |
| Theta range for data collection | 4.24 to 27.50°. | |
| Index ranges | -10<=h<=10, -7<=k<=7, -19<=l<=19 | |
| Reflections collected | 15378 | |
| Independent reflections | 3230 [R(int) = 0.0268] | |
| Completeness to theta = 27.50° | 98.5 % | |
| Absorption correction | None | |
| Max. and min. transmission | 0.9888 and 0.9836 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3230 / 1 / 158 | |
| Goodness-of-fit on $F^2$ | 1.045 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0327, wR2 = 0.0830 | |
| R indices (all data) | R1 = 0.0355, wR2 = 0.0849 | |
| Absolute structure parameter | -0.3(10) | |
| Extinction coefficient | 0.060(16) | |

| | |
|---|---|
| Largest diff. peak and hole | 0.162 and -0.122 e.Å$^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)

for h03sdb01. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7905(1) | -918(1) | 1889(1) | 27(1) |
| N(1) | 7203(1) | 1175(2) | 592(1) | 28(1) |
| C(1) | 7805(1) | 1005(2) | 2443(1) | 23(1) |
| C(2) | 9442(1) | 2250(2) | 2570(1) | 28(1) |
| C(3) | 9427(1) | 4247(2) | 3176(1) | 28(1) |
| C(4) | 9027(2) | 3555(2) | 4094(1) | 34(1) |
| C(5) | 7396(2) | 2256(2) | 3964(1) | 31(1) |
| C(6) | 7429(1) | 240(2) | 3358(1) | 24(1) |
| C(7) | 11068(2) | 5495(2) | 3301(1) | 42(1) |
| C(8) | 5838(1) | -1174(2) | 3246(1) | 27(1) |
| C(9) | 5550(2) | -1996(2) | 4170(1) | 38(1) |
| C(10) | 4264(2) | -61(3) | 2709(1) | 44(1) |
| C(11) | 7643(1) | -633(2) | 958(1) | 25(1) |
| C(12) | 7971(2) | -2733(2) | 505(1) | 32(1) |
| C(13) | 8097(2) | -2332(2) | -494(1) | 35(1) |
| C(14) | 6715(2) | -779(2) | -931(1) | 37(1) |
| C(15) | 6930(2) | 1360(2) | -415(1) | 32(1) |

Table 3. Bond lengths [Å] and angles [°] for h03sdb01.

| | | | |
|---|---|---|---|
| O(1)-C(11) | 1.3673(13) | C(7)-H(7C) | 0.9800 |
| O(1)-C(1) | 1.4528(13) | C(8)-C(9) | 1.5259(16) |
| N(1)-C(11) | 1.2578(16) | C(8)-C(10) | 1.5271(17) |
| N(1)-C(15) | 1.4715(14) | C(8)-H(8) | 1.0000 |
| C(1)-C(2) | 1.5171(15) | C(9)-H(9A) | 0.9800 |
| C(1)-C(6) | 1.5283(14) | C(9)-H(9B) | 0.9800 |
| C(1)-H(1) | 1.0000 | C(9)-H(9C) | 0.9800 |
| C(2)-C(3) | 1.5251(17) | C(10)-H(10A) | 0.9800 |
| C(2)-H(2A) | 0.9900 | C(10)-H(10B) | 0.9800 |
| C(2)-H(2B) | 0.9900 | C(10)-H(10C) | 0.9800 |
| C(3)-C(7) | 1.5212(17) | C(11)-C(12) | 1.5060(15) |
| C(3)-C(4) | 1.5261(17) | C(12)-C(13) | 1.5278(17) |
| C(3)-H(3) | 1.0000 | C(12)-H(12A) | 0.9900 |
| C(4)-C(5) | 1.5299(17) | C(12)-H(12B) | 0.9900 |
| C(4)-H(4A) | 0.9900 | C(13)-C(14) | 1.5192(19) |
| C(4)-H(4B) | 0.9900 | C(13)-H(13A) | 0.9900 |
| C(5)-C(6) | 1.5356(15) | C(13)-H(13B) | 0.9900 |
| C(5)-H(5A) | 0.9900 | C(14)-C(15) | 1.5152(18) |
| C(5)-H(5B) | 0.9900 | C(14)-H(14A) | 0.9900 |
| C(6)-C(8) | 1.5428(15) | C(14)-H(14B) | 0.9900 |
| C(6)-H(6) | 1.0000 | C(15)-H(15A) | 0.9900 |
| C(7)-H(7A) | 0.9800 | C(15)-H(15B) | 0.9900 |
| C(7)-H(7B) | 0.9800 | | |

| | |
|---|---|
| C(11)-O(1)-C(1) | 116.94(8) |
| C(11)-N(1)-C(15) | 118.57(10) |
| O(1)-C(1)-C(2) | 109.39(8) |
| O(1)-C(1)-C(6) | 107.29(8) |
| C(2)-C(1)-C(6) | 112.12(9) |
| O(1)-C(1)-H(1) | 109.3 |
| C(2)-C(1)-H(1) | 109.3 |
| C(6)-C(1)-H(1) | 109.3 |
| C(1)-C(2)-C(3) | 111.55(9) |
| C(1)-C(2)-H(2A) | 109.3 |
| C(3)-C(2)-H(2A) | 109.3 |
| C(1)-C(2)-H(2B) | 109.3 |
| C(3)-C(2)-H(2B) | 109.3 |
| H(2A)-C(2)-H(2B) | 108.0 |
| C(7)-C(3)-C(2) | 111.44(10) |
| C(7)-C(3)-C(4) | 112.05(10) |
| C(2)-C(3)-C(4) | 109.34(10) |
| C(7)-C(3)-H(3) | 108.0 |
| C(2)-C(3)-H(3) | 108.0 |
| C(4)-C(3)-H(3) | 108.0 |
| C(3)-C(4)-C(5) | 111.84(10) |
| C(3)-C(4)-H(4A) | 109.2 |
| C(5)-C(4)-H(4A) | 109.2 |
| C(3)-C(4)-H(4B) | 109.2 |
| C(5)-C(4)-H(4B) | 109.2 |
| H(4A)-C(4)-H(4B) | 107.9 |
| C(4)-C(5)-C(6) | 112.18(10) |
| C(4)-C(5)-H(5A) | 109.2 |
| C(6)-C(5)-H(5A) | 109.2 |
| C(4)-C(5)-H(5B) | 109.2 |
| C(6)-C(5)-H(5B) | 109.2 |
| H(5A)-C(5)-H(5B) | 107.9 |
| C(1)-C(6)-C(5) | 107.62(9) |
| C(1)-C(6)-C(8) | 113.26(9) |

| | |
|---|---|
| C(5)-C(6)-C(8) | 113.84(9) |
| C(1)-C(6)-H(6) | 107.3 |
| C(5)-C(6)-H(6) | 107.3 |
| C(8)-C(6)-H(6) | 107.3 |
| C(3)-C(7)-H(7A) | 109.5 |
| C(3)-C(7)-H(7B) | 109.5 |
| H(7A)-C(7)-H(7B) | 109.5 |
| C(3)-C(7)-H(7C) | 109.5 |
| H(7A)-C(7)-H(7C) | 109.5 |
| H(7B)-C(7)-H(7C) | 109.5 |
| C(9)-C(8)-C(10) | 110.51(11) |
| C(9)-C(8)-C(6) | 111.73(10) |
| C(10)-C(8)-C(6) | 113.70(10) |
| C(9)-C(8)-H(8) | 106.8 |
| C(10)-C(8)-H(8) | 106.8 |
| C(6)-C(8)-H(8) | 106.8 |
| C(8)-C(9)-H(9A) | 109.5 |
| C(8)-C(9)-H(9B) | 109.5 |
| H(9A)-C(9)-H(9B) | 109.5 |
| C(8)-C(9)-H(9C) | 109.5 |
| H(9A)-C(9)-H(9C) | 109.5 |
| H(9B)-C(9)-H(9C) | 109.5 |
| C(8)-C(10)-H(10A) | 109.5 |
| C(8)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| C(8)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| N(1)-C(11)-O(1) | 121.48(10) |
| N(1)-C(11)-C(12) | 128.84(10) |
| O(1)-C(11)-C(12) | 109.68(10) |
| C(11)-C(12)-C(13) | 110.40(10) |
| C(11)-C(12)-H(12A) | 109.6 |
| C(13)-C(12)-H(12A) | 109.6 |

| | |
|---|---|
| C(11)-C(12)-H(12B) | 109.6 |
| C(13)-C(12)-H(12B) | 109.6 |
| H(12A)-C(12)-H(12B) | 108.1 |
| C(14)-C(13)-C(12) | 109.00(10) |
| C(14)-C(13)-H(13A) | 109.9 |
| C(12)-C(13)-H(13A) | 109.9 |
| C(14)-C(13)-H(13B) | 109.9 |
| C(12)-C(13)-H(13B) | 109.9 |
| H(13A)-C(13)-H(13B) | 108.3 |
| C(15)-C(14)-C(13) | 109.33(10) |
| C(15)-C(14)-H(14A) | 109.8 |
| C(13)-C(14)-H(14A) | 109.8 |
| C(15)-C(14)-H(14B) | 109.8 |
| C(13)-C(14)-H(14B) | 109.8 |
| H(14A)-C(14)-H(14B) | 108.3 |
| N(1)-C(15)-C(14) | 115.14(10) |
| N(1)-C(15)-H(15A) | 108.5 |
| C(14)-C(15)-H(15A) | 108.5 |
| N(1)-C(15)-H(15B) | 108.5 |
| C(14)-C(15)-H(15B) | 108.5 |
| H(15A)-C(15)-H(15B) | 107.5 |

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for h03sdb01. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 37(1) | 22(1) | 24(1) | -2(1) | 10(1) | 1(1) |
| N(1) | 32(1) | 29(1) | 25(1) | -1(1) | 8(1) | -1(1) |
| C(1) | 27(1) | 21(1) | 23(1) | -1(1) | 8(1) | 0(1) |
| C(2) | 26(1) | 28(1) | 31(1) | 0(1) | 10(1) | -3(1) |
| C(3) | 27(1) | 25(1) | 32(1) | 1(1) | 5(1) | -2(1) |
| C(4) | 40(1) | 32(1) | 29(1) | -6(1) | 5(1) | -8(1) |
| C(5) | 37(1) | 33(1) | 27(1) | -5(1) | 13(1) | -5(1) |
| C(6) | 26(1) | 23(1) | 23(1) | 1(1) | 6(1) | 0(1) |
| C(7) | 35(1) | 38(1) | 52(1) | -4(1) | 9(1) | -11(1) |
| C(8) | 28(1) | 26(1) | 28(1) | 2(1) | 9(1) | -2(1) |
| C(9) | 43(1) | 40(1) | 35(1) | 4(1) | 15(1) | -10(1) |
| C(10) | 28(1) | 43(1) | 59(1) | 15(1) | 2(1) | -5(1) |
| C(11) | 25(1) | 28(1) | 24(1) | -4(1) | 9(1) | -4(1) |
| C(12) | 40(1) | 27(1) | 34(1) | -5(1) | 14(1) | -1(1) |
| C(13) | 42(1) | 35(1) | 31(1) | -9(1) | 14(1) | -4(1) |
| C(14) | 41(1) | 41(1) | 28(1) | -6(1) | 7(1) | -8(1) |
| C(15) | 36(1) | 34(1) | 25(1) | 0(1) | 6(1) | -2(1) |

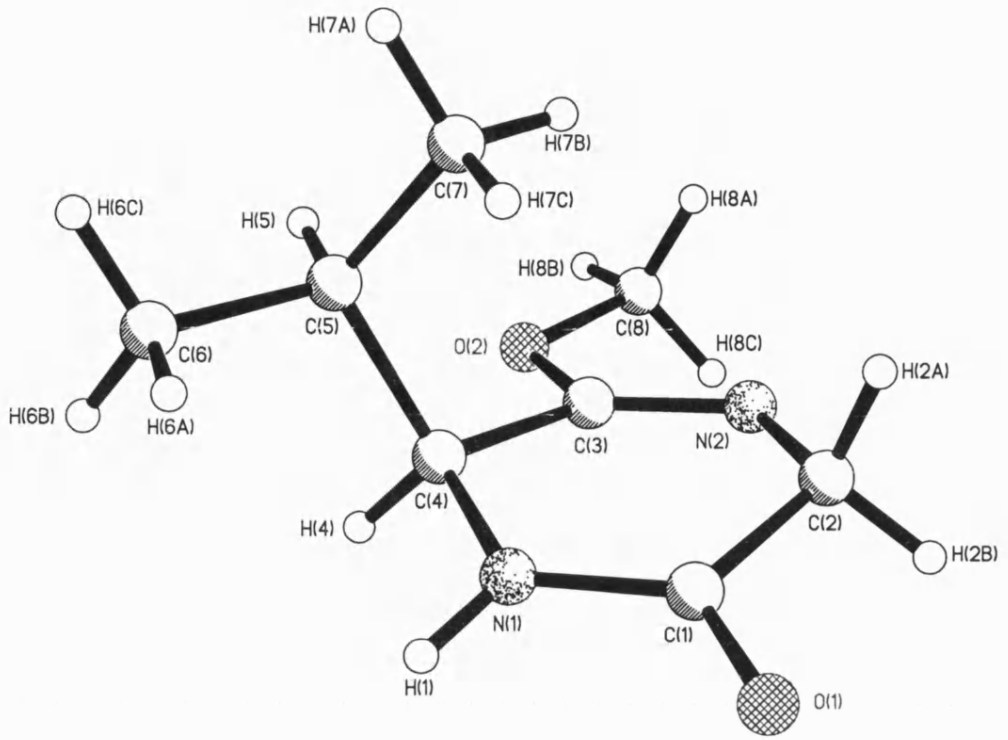



Table 1. Crystal data and structure refinement for h04sdb01.

| | | |
|---|---|---|
| Identification code | h04sdb01 | |
| Empirical formula | C8 H14 N2 O2 | |
| Formula weight | 170.21 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_1\ 2_1\ 2_1$ | |
| Unit cell dimensions | a = 6.2600(3) Å | □= 90°. |
| | b = 6.3070(11) Å | □= 90°. |
| | c = 23.8840(3) Å | □ = 90°. |
| Volume | 942.98(17) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.199 $Mg/m^3$ | |

| | |
|---|---|
| Absorption coefficient | 0.087 $mm^{-1}$ |
| F(000) | 368 |
| Crystal size | 0.17 x 0.13 x 0.10 $mm^3$ |
| Theta range for data collection | 3.67 to 27.48°. |
| Index ranges | -8<=h<=5, -7<=k<=8, -23<=l<=30 |
| Reflections collected | 5090 |
| Independent reflections | 2030 [R(int) = 0.0519] |
| Completeness to theta = 27.48° | 97.4 % |
| Absorption correction | None |
| Max. and min. transmission | 0.9914 and 0.9849 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2030 / 0 / 117 |
| Goodness-of-fit on $F^2$ | 1.023 |
| Final R indices [I>2sigma(I)] | R1 = 0.0483, wR2 = 0.1061 |
| R indices (all data) | R1 = 0.0919, wR2 = 0.1197 |
| Absolute structure parameter | -1(2) |
| Extinction coefficient | 0.054(16) |
| Largest diff. peak and hole | 0.300 and -0.332 $e.Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)

for h04sdb01. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | -5239(3) | -5276(2) | -2960(1) | 47(1) |
| O(2) | -4280(3) | 887(2) | -4466(1) | 41(1) |
| N(1) | -4326(3) | -1873(3) | -3154(1) | 30(1) |
| N(2) | -4785(3) | -2638(2) | -4311(1) | 32(1) |
| C(1) | -4788(4) | -3863(3) | -3299(1) | 32(1) |
| C(2) | -4794(4) | -4386(3) | -3913(1) | 37(1) |
| C(3) | -4319(3) | -840(3) | -4127(1) | 28(1) |
| C(4) | -3715(3) | -195(3) | -3540(1) | 27(1) |
| C(5) | -1315(4) | 350(4) | -3516(1) | 46(1) |
| C(6) | -699(4) | 1243(4) | -2956(1) | 57(1) |
| C(7) | 70(4) | -1532(4) | -3677(1) | 75(1) |
| C(8) | -4703(5) | 480(4) | -5049(1) | 55(1) |

Table 3. Bond lengths [Å] and angles [°] for h04sdb01.

| | | | |
|---|---|---|---|
| O(1)-C(1) | 1.238(2) | C(4)-H(4) | 1.0000 |
| O(2)-C(3) | 1.358(2) | C(5)-C(6) | 1.501(3) |
| O(2)-C(8) | 1.441(3) | C(5)-C(7) | 1.519(3) |
| N(1)-C(1) | 1.334(3) | C(5)-H(5) | 1.0000 |
| N(1)-C(4) | 1.455(3) | C(6)-H(6A) | 0.9800 |
| N(1)-H(1) | 0.89(3) | C(6)-H(6B) | 0.9800 |
| N(2)-C(3) | 1.251(2) | C(6)-H(6C) | 0.9800 |
| N(2)-C(2) | 1.457(2) | C(7)-H(7A) | 0.9800 |
| C(1)-C(2) | 1.501(3) | C(7)-H(7B) | 0.9800 |
| C(2)-H(2A) | 0.9900 | C(7)-H(7C) | 0.9800 |
| C(2)-H(2B) | 0.9900 | C(8)-H(8A) | 0.9800 |
| C(3)-C(4) | 1.506(3) | C(8)-H(8B) | 0.9800 |
| C(4)-C(5) | 1.543(3) | C(8)-H(8C) | 0.9800 |

| | | | |
|---|---|---|---|
| C(3)-O(2)-C(8) | 115.49(16) | N(1)-C(4)-C(3) | 109.08(15) |
| C(1)-N(1)-C(4) | 125.20(18) | N(1)-C(4)-C(5) | 113.23(17) |
| C(1)-N(1)-H(1) | 119.1(13) | C(3)-C(4)-C(5) | 109.86(16) |
| C(4)-N(1)-H(1) | 115.6(13) | N(1)-C(4)-H(4) | 108.2 |
| C(3)-N(2)-C(2) | 117.15(17) | C(3)-C(4)-H(4) | 108.2 |
| O(1)-C(1)-N(1) | 123.82(19) | C(5)-C(4)-H(4) | 108.2 |
| O(1)-C(1)-C(2) | 118.71(18) | C(6)-C(5)-C(7) | 111.8(2) |
| N(1)-C(1)-C(2) | 117.46(18) | C(6)-C(5)-C(4) | 111.5(2) |
| N(2)-C(2)-C(1) | 118.13(16) | C(7)-C(5)-C(4) | 111.86(19) |
| N(2)-C(2)-H(2A) | 107.8 | C(6)-C(5)-H(5) | 107.1 |
| C(1)-C(2)-H(2A) | 107.8 | C(7)-C(5)-H(5) | 107.1 |
| N(2)-C(2)-H(2B) | 107.8 | C(4)-C(5)-H(5) | 107.1 |
| C(1)-C(2)-H(2B) | 107.8 | C(5)-C(6)-H(6A) | 109.5 |
| H(2A)-C(2)-H(2B) | 107.1 | C(5)-C(6)-H(6B) | 109.5 |
| N(2)-C(3)-O(2) | 121.41(17) | H(6A)-C(6)-H(6B) | 109.5 |
| N(2)-C(3)-C(4) | 129.10(17) | C(5)-C(6)-H(6C) | 109.5 |
| O(2)-C(3)-C(4) | 109.48(16) | H(6A)-C(6)-H(6C) | 109.5 |

| | |
|---|---|
| H(6B)-C(6)-H(6C) | 109.5 |
| C(5)-C(7)-H(7A) | 109.5 |
| C(5)-C(7)-H(7B) | 109.5 |
| H(7A)-C(7)-H(7B) | 109.5 |
| C(5)-C(7)-H(7C) | 109.5 |
| H(7A)-C(7)-H(7C) | 109.5 |
| H(7B)-C(7)-H(7C) | 109.5 |
| O(2)-C(8)-H(8A) | 109.5 |
| O(2)-C(8)-H(8B) | 109.5 |
| H(8A)-C(8)-H(8B) | 109.5 |
| O(2)-C(8)-H(8C) | 109.5 |
| H(8A)-C(8)-H(8C) | 109.5 |
| H(8B)-C(8)-H(8C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for h04sdb01. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

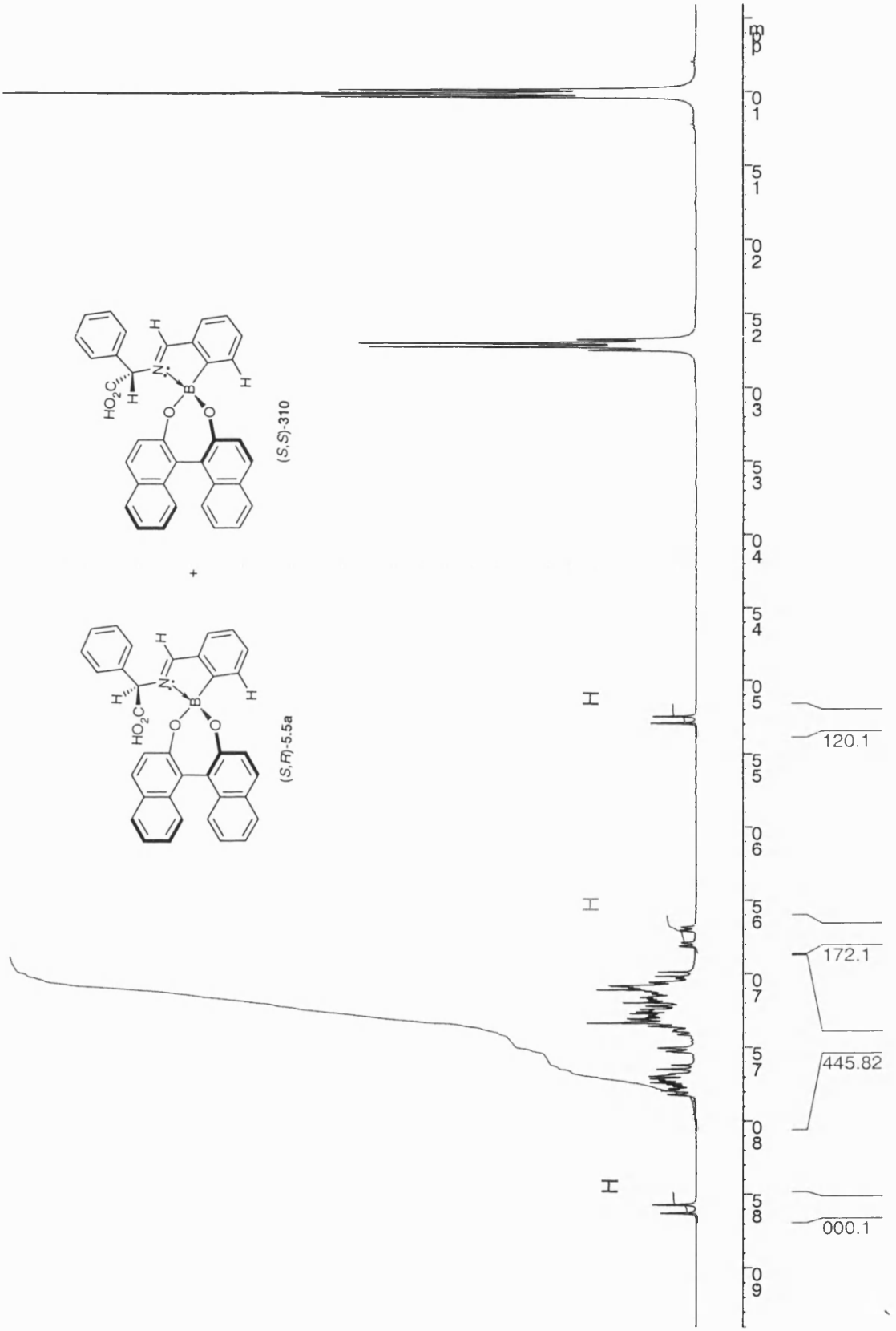
| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 77(1) | 34(1) | 29(1) | 8(1) | 8(1) | 3(1) |
| O(2) | 67(1) | 27(1) | 29(1) | 3(1) | 0(1) | -1(1) |
| N(1) | 41(1) | 31(1) | 19(1) | -2(1) | -1(1) | 4(1) |
| N(2) | 47(1) | 23(1) | 25(1) | 1(1) | 0(1) | -2(1) |
| C(1) | 40(1) | 30(1) | 27(1) | 0(1) | 2(1) | 8(1) |
| C(2) | 57(1) | 28(1) | 25(1) | 0(1) | 2(1) | -1(1) |
| C(3) | 34(1) | 28(1) | 22(1) | 3(1) | 3(1) | 4(1) |
| C(4) | 31(1) | 24(1) | 27(1) | -2(1) | 1(1) | 2(1) |
| C(5) | 36(1) | 56(2) | 45(1) | -12(1) | 2(1) | -7(1) |
| C(6) | 43(1) | 64(2) | 63(2) | -10(1) | -14(1) | -6(1) |
| C(7) | 29(1) | 104(2) | 90(2) | -44(2) | 0(1) | 15(2) |
| C(8) | 98(2) | 43(1) | 23(1) | 8(1) | -6(1) | -2(1) |

Table 5. Hydrogen bonds for h04sdb01 [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(1) ...O(1#) | 0.89(3) | 1.975(3) | 2.859(2) | 173.42(15) |

# Chapter 8

# Appendix B


(S,S)-310
+
(S,R)-5.5a
H
H
H
120.1
172.1
445.82
000.1

# Chapter 9

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